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ABSTRACT

These hearings before the House of Representatives Committee on Government Reform address possible reasons for the apparently rapid increase in the incidence of autism. An introduction by the Committee Chairman, Dan Burton, provides background information and suggests a possible linkage between autism and the mumps-measles-rubella vaccine, specifically the possibility of mercury contamination. Text is included of statements from representatives of the following: the Committee on Immunization Safety, Institute of Medicine; National Academy of Sciences; Indiana University School of Medicine; McGill University; MIND Institute, University of California, Davis; National Institute of Child Health and Human Development; Office of Vaccine Research and Review, Food and Drug Administration; Office of Vital Statistics and Epidemiology; and the Center on Birth Defects and Developmental Disabilities. Extensive letters, statements, and other materials are also included. (DB)

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AUTISM—WHY THE INCREASED RATES? A ONE-YEAR UPDATE

ED 467 484

HEARINGS

BEFORE THE

COMMITTEE ON GOVERNMENT REFORM

HOUSE OF REPRESENTATIVES

ONE HUNDRED SEVENTH CONGRESS

FIRST SESSION

APRIL 25 AND 26, 2001

Serial No. 107–29

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AUTISM—WHY THE INCREASED RATES? A ONE-YEAR UPDATE

WEDNESDAY, APRIL 25, 2001

House of Representatives,
Committee on Government Reform,
Washington, DC.

The committee met, pursuant to notice, at 11:07 a.m., in room 2154, Rayburn House Office Building, Hon. Dan Burton (chairman of the committee) presiding.

Present: Representatives Burton, Morella, Ros-Lehtinen, Horn, Davis, Weldon, Waxman, Maloney, Norton, Cummings, Kucinich, Blagojevich, Tierney, Schakowsky, and Clay.

Staff present: David A. Kass, deputy counsel and parliamentarian; Mark Corallo, director of communications; John Callendar, counsel; S. Elizabeth Clay, Nicole Petrosino, and John Rowe, professional staff members; Robert A. Briggs, chief clerk; Robin Butler, office manager; Michael Canty and Toni Lightle, legislative assistants; Scott Fagan, staff assistant; Leneal Scott, computer systems manager; John Sare, deputy chief clerk; Corinne Zaccagnini, systems administrator; Phil Barnett, minority chief counsel; Kate Anderson and Sarah Despres, minority counsels; Ellen Rayner, minority chief clerk; and Jean Gosa, minority assistant clerk.

Mr. Burton. Good morning.

A quorum being present, the Committee on Government Reform will come to order. I ask unanimous consent that all Members' and witnesses' written and opening statements be included in the record. Without objection, so ordered.

I ask unanimous consent that all articles, exhibits, or extraneous or tabular material referred to be included in the record. Without objection, so ordered.

During the 106th Congress, I initiated oversight investigations to look at the dramatic rise in autism rates and the many concerns about vaccine safety. Autism rates have skyrocketed. Conservative estimates suggest 1 in 500 children in the United States is autistic. However, those rates are dramatically higher in some places such as Brick Township, NJ, where the rates are 1 in 150. I think Congressman Smith, who is going to testify today, represents part of that area.

In the first quarter of this year a child was diagnosed with autism every 3 hours in California. Last year, that rate was every 6 hours. Look at that graph. They are having an absolute epidemic out there.

Indiana is seeing a similar trend in increased rates; 1 in 400 children in my home State is autistic. Between December 1999 and De-

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cember 2000, requests for special education services for children with autism went up 25 percent. That is a 25-percent increase in requests for taxpayer-provided services in just a year.

We have a national and potentially worldwide epidemic on our hands. It cannot simply be better reporting or an expanded definition of autism. There has to be more to it than that.

As with any epidemic, we need to focus significant energy and research on containing it. We need to locate the cause or causes. We need to determine if this is the same condition we understand autism to be or not. Could this epidemic of children who regress into "autism" be another condition being called autism?

We need to be aggressive in developing and making available appropriate treatments for both the behavioral issues and the biomedical illnesses related to this condition. And we need to provide credible and timely information to the public. Has the public health sector responded adequately and appropriately to this epidemic? We will be hearing from witnesses over the next 2 days to find out.

Autism, or Autism Spectrum Disorder, is devastating to families. I know this from personal experience. My grandson, Christian, was born healthy and developed normally. His story is not much different than that of the thousands of families we have heard from over the last year. He met his developmental milestones. He was talkative. He enjoyed being with people. He interacted socially.

Then Christian received his routine immunizations as recommended by the Centers for Disease Control and Prevention and his life changed dramatically and very rapidly. We now know that through his shots, he may have been exposed to 41 times the level of mercury than is considered safe by Federal guidelines for a child his size. This was on top of other mercury exposure from earlier vaccinations.

Within 10 days of receiving his vaccines, Christian was locked into the world of autism—within 10 days. Is it related to the MMR vaccine? Is it related to the mercury toxicity? Is it the environment, including food allergies? Or is autism purely genetic? Some would have us believe that a child's regression into autism within a short time of vaccination is purely a coincidence. I ask those individuals to show me the science that proves this theory.

On Monday, the "Measles-Mumps-Rubella Vaccine and Autism Report" was released by the Institute of Medicine's Committee on Immunization Safety Review. We have Dr. Marie McCormick, the Chair of this committee, here today to talk about the findings and recommendations of the report.

I realize the headlines over the last 3 days have said that the committee found no connection between the MMR vaccine and autism. I would urge all of you to read the entire report and recognize that the committee found that there was insufficient evidence to conclusively prove or disprove a connection between the MMR vaccine and acquired autism. And yet, on television all across this country, every parent saw that there was no connection between the MMR vaccine and autism.

Yet, that is not what the report said. I believe a disservice has been given to the American people about this. Parents need to know the risks involved with certain exposures their children have to face. And they need to have all the facts, not part of the facts.

It should be noted that the committee notes in its conclusions that it could not exclude the possibility that MMR vaccine could contribute to Autism Spectrum Disorder.

In the scientific community, there is an accepted hierarchy of research methodology that builds a balanced foundation of the evidence. That is in attachment 1. What we learned from the Institute of Medicine is that the research has not yet been conducted to build this hierarchy of evidence regarding the question of whether or not the MMR vaccine may be linked to the increased incidence of autism.

We have substantial parental observation, which should never be discounted. And we have several case studies and laboratory evidence showing measles virus in the guts of autistic children who have bowel dysfunction. And we also have several population-level epidemiological studies.

While the Immunization Committee noted that the epidemiologic studies do not support an association at a population level, their report stated that "it is important to recognize the inherent methodological limitations of such studies in establishing causality."

In essence, the studies that have been published and held up by the public health community as "proof" against Dr. Wakefield's hypothesis can never answer the question of whether or not MMR vaccine is linked to autism in some children. We do not have enough research to make an evidence-based final conclusion. What we have is a clear indication that a problem exists for some children. We need to do the research to get our arms around that problem, so that we can prevent any further escalation of this epidemic of acquired autism.

When the Institute of Medicine formed their committee, we were assured that there would be no one on the committee who had ties to the vaccine industry. We were told there would be nobody connected to the vaccine industry involved in the research done by this committee. So I was disturbed to learn that the committee sent this report out for review and comment prior to becoming final to numerous individuals who have ties to the vaccine industry, including the manufacturer of the MMR vaccine.

They sent it out for critiquing, and there were changes made by these other people outside. They also sent it to at least one individual who presented to the committee, but not to Dr. Wakefield and the rest of the presenters. This preferential treatment is disturbing, and I would like to know why they did not send it to everybody who was a presenter.

I am including in the record a letter I received from one of the reviewers, and a previous witness to this committee regarding his concerns about flaws in the evaluation of the published research. He is with the University of Oklahoma, the Health Center. And that will be included in the record.

[The information referred to follows:]

The University of Oklahoma
Health Sciences Center
DEPARTMENT OF MICROBIOLOGY AND IMMUNOLOGY

April 24, 2001

Congressman Dan Burton
Chairman
Committee on Government Reform
House of Representatives
Congress of the United States.
2157 Rayburn House Office Building
Washington D.C. 20515-6143

Dear Chairman Burton:

I am writing this letter to express my concern with regards to the Report by the Institute of Medicine involving the association of the Measles, Mumps Rubella Vaccine and Autism. I was an external reviewer of the Institute's report. Upon review, I found severe problems and concerns with the panel report. I provided a 5-page critique of the report to the Institute of Medicine and I am concern that my critique was not considered in the release of the final report. I will briefly summarize my major concerns below.

The report highly criticizes the peer-review publications that cite a casual association of the MMR vaccine and autism and does not provide a similar critique of the peer review publications that cite a lack of association of the MMR vaccine and autism. The report itself appears to present a biased opinion in the initial discussion.

Several of the peer review publications that cite a lack of association of the MMR vaccine and autism after careful re-evaluation have a number of problems and bias associated with their data and the analysis of the data.
1) Mistakes in calculations not caught by the authors, the journal reviewers or the journal editors.
2) Potentially inappropriate manipulation of the data and the use of improper statistical methods to demonstrate a lack of. association between MMR vaccination and autism.
3) Some data that suggests a statistically significant association at one time point between parental concern for behavior changes (e.g. autism) and the MMR vaccine is stated to be an artifact. Indeed, the authors comment that this particular data is an artifact. This statement appears biased.
4) Exclusion criteria for data to be analyzed could be biased.

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5) One of the publications includes the lack of autism and the MMR vaccine in the title of the paper, yet no data on autism is presented in the text of the paper. This is misleading.
6) One of the publications that are used to support the lack of the MMR vaccine and autism cites support of Merck and Company in the acknowledgements. This is not mentioned in the Institute's report and could be considered potentially as a pre-existing bias.

I could continue to list my problems with the Institute's report, however, I feel that my evaluation may have been completely ignored. I very much appreciate your time and consideration regarding this matter and would be happy to provide you with my detailed critique of the report.

Sincerely,

Ronald C. Kennedy

Ronald C. Kennedy, Ph.D.
Professor

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Mr. BURTON. I want to read just one part of his letter.

"The report highly criticizes the peer review publications that cite a causal association of the MMR vaccine and autism and does not provide a similar critique of the peer review publications that cite a lack of association of the MMR vaccine and autism."

It also says, "One of the publications that are used to support the lack of the MMR vaccine and autism cites support of Merck and Company in the acknowledgements." They are the producer of the MMR vaccine.

This is not mentioned in the Institute's report and could be considered potentially as a pre-existing bias. We want to ask the person who is going to be testifying about the report why that happened.

They also sent it to at least one individual who presented to the committee, but not Wakefield.

I am including in the record this letter I received from the reviewer about what he believes to be the flaws in the evaluation of the published research. He also raises concerns about the lack of the Institute's acknowledgement in their evaluation that one of the publications used to support a lack of a connection between the MMR vaccine and autism was sponsored by Merck, the manufacturer of the MMR vaccine.

We have a very long hearing today. I am going to ask the witnesses to stick to the time limit so we can get through all the panels and have time for questions. We will be hearing first from my colleagues and friends, the chairmen of the Autism Congressional Caucus—which I am proud to be a member of—Congressman Christopher Smith of New Jersey, and Congressman Mike Doyle of Pennsylvania.

The record will remain open until May 11.

I apologize to Mr. Waxman for talking so long, but I feel very strongly, as you know.

Mr. Waxman, you are recognized for an opening statement.

[The prepared statement of Hon. Dan Burton follows:]

Opening Statement

Chairman Dan Burton
Government Reform Committee

Hearing

Autism - Why the Increased Rates? A One Year Update. Part I

Wednesday, April 25, 2001

2154 Rayburn House Office Building
Washington, DC 20515

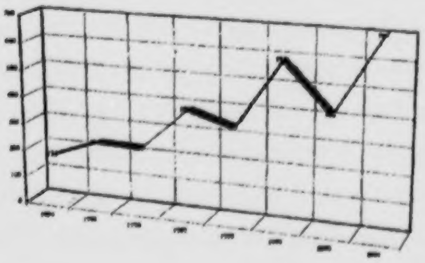
Good morning, a Quorum being present, the Committee on Government Reform will come to order. I ask unanimous consent that all Members' and witnesses' written and opening statements be included in the record. Without objection, so ordered.

I ask unanimous consent that all articles, exhibits, and extraneous or tabular material referred to be included in the record. Without objection, so ordered.

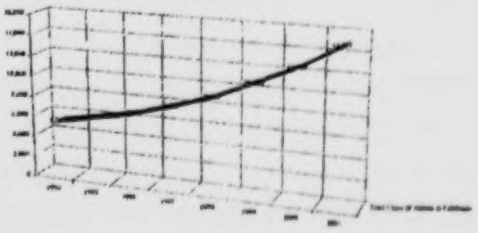
[Chairman's Opening Statement]
During the 106th Congress, I initiated oversight investigations to look at the dramatic rise in autism rates and the many concerns about vaccine safety.

Autism rates have skyrocketed. Conservative estimates suggest 1 in 500 children in the United States is autistic. However, those rates are dramatically higher in some places such as Brick Township, New Jersey, where the rates are 1 in 150.

In the first quarter of this year a child was diagnosed with autism every three hours in California. Last year, that rate was every six hours.



Children Diagnosed with Autism the First Quarter of Each Year in California



Total Cases of Autism in California

Indiana is seeing a similar trend in increased rates. One in 400 children in Indiana is autistic. Between December 1999 and December 2000, requests for special education services for children with autism went up twenty-five percent. That is a twenty-five percent increase in requests for taxpayer provided services in one year.

We have a national and potentially world-wide epidemic on our hands. It cannot simply be better reporting or an expanded definition of autism.

As with any epidemic, we need to focus significant energy and research on containing it. We need to locate the cause or causes. We need to determine if this is the same condition we understand autism to be or not. Could this epidemic of children who regress into "autism" be another condition being called autism?

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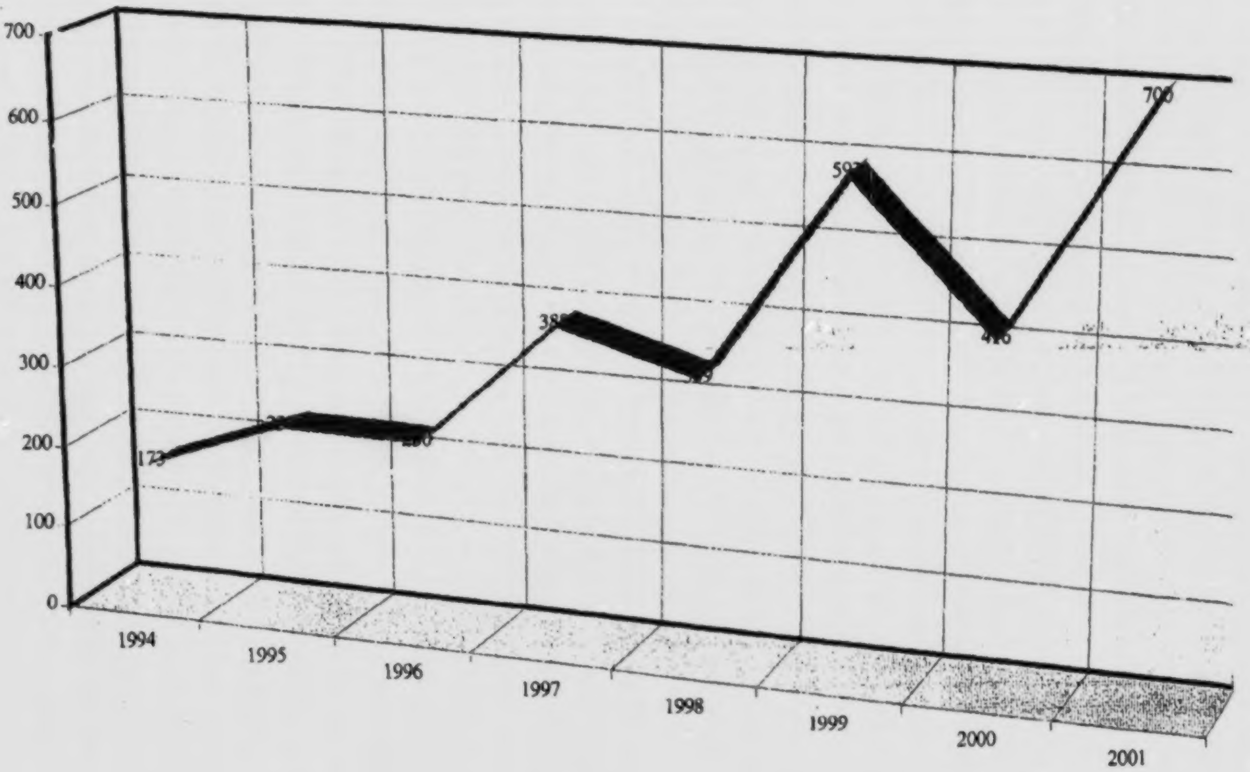
We have a very long hearing today. I am going to ask the witnesses to stick to the time limit so we can get through all the panels and have time for questions.

We will be hearing first from my colleagues and friends, the Chairmen of the Autism Congressional Caucus, which I am proud to be a member of, Congressman Christopher Smith of New Jersey, and Congressman Mike Doyle of Pennsylvania.

The record will remain open until May 11.

I now recognize the ranking minority member, Mr. Waxman for his opening statement.

Children Diagnosed with Autism the First Quarter of Each Year in California



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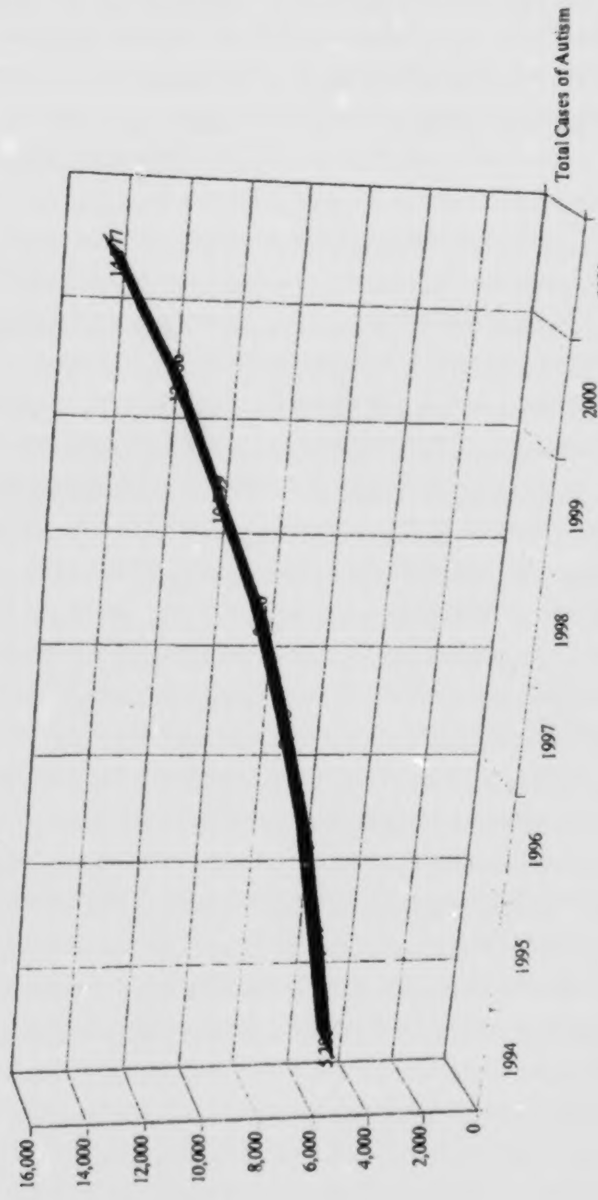
Total Cases of Autism in California



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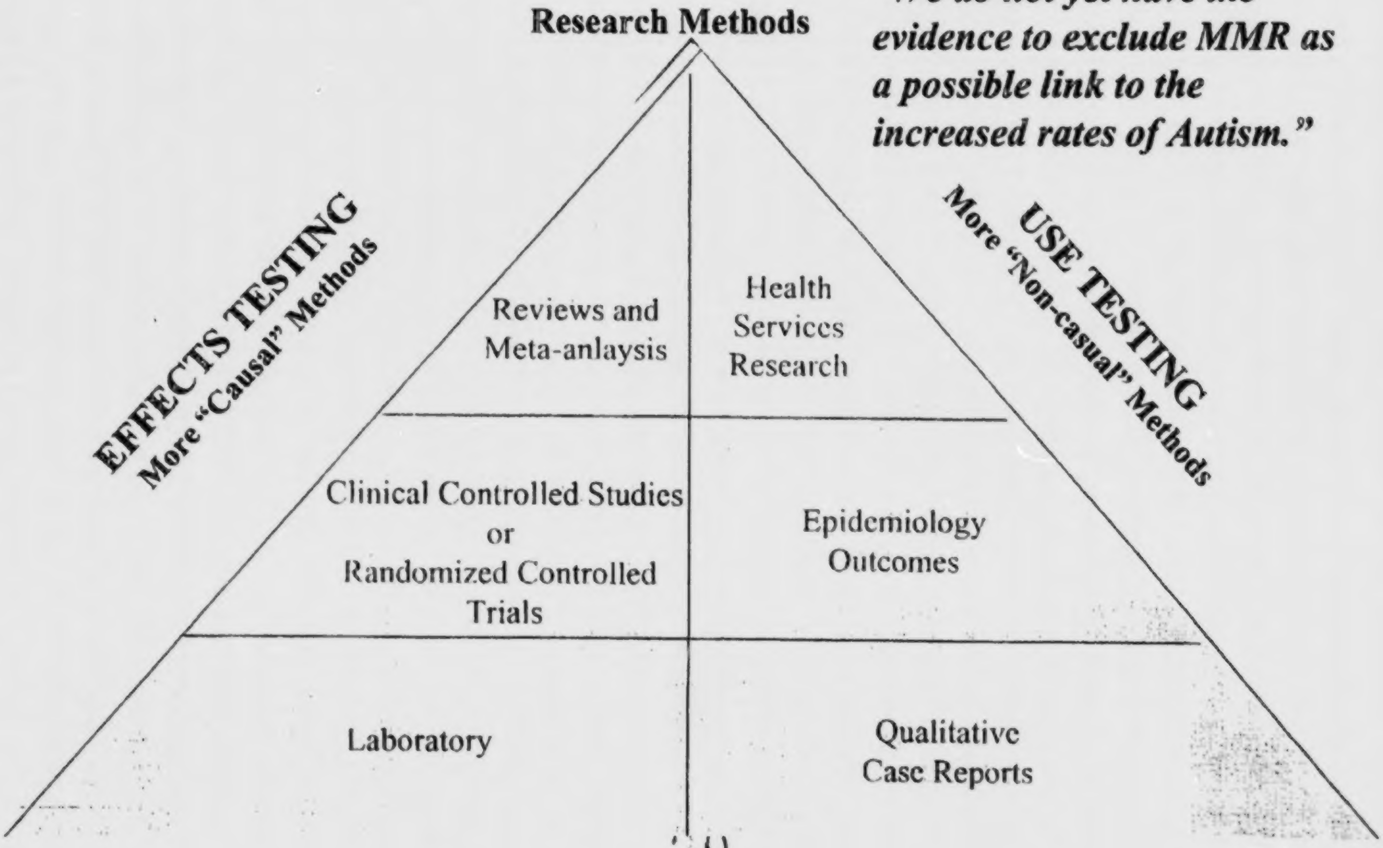
"Balanced" Evidence Hierarchy

"We do not yet have the evidence to exclude MMR as a possible link to the increased rates of Autism."



Research Methods

EFFECTS TESTING
More "Causal" Methods

USE TESTING
More "Non-casual" Methods

Reviews and
Meta-anlaysis

Health
Services
Research

Clinical Controlled Studies
or
Randomized Controlled
Trials

Epidemiology
Outcomes

Laboratory

Qualitative
Case Reports

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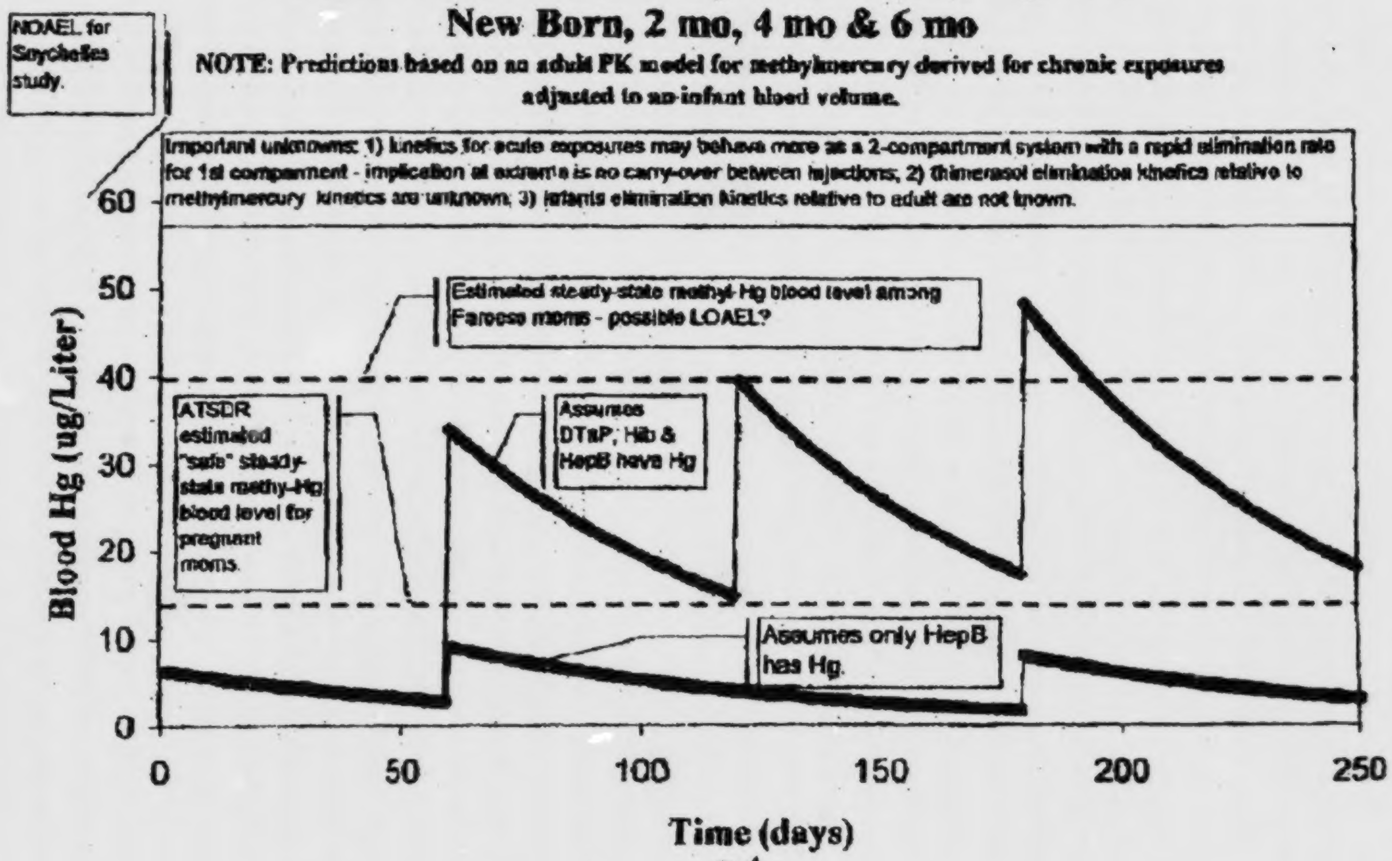
Predicted Infant Blood Hg from Vaccine Injections

New Born, 2 mo, 4 mo & 6 mo

NOTE: Predictions based on an adult PK model for methylmercury derived for chronic exposures adjusted to an infant blood volume.



Important unknowns: 1) kinetics for acute exposures may behave more as a 2-compartment system with a rapid elimination rate for 1st compartment - implication at extreme is no carry-over between injections; 2) thimerasol elimination kinetics relative to methylmercury kinetics are unknown; 3) infants elimination kinetics relative to adult are not known.

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Mr. WAXMAN. Thank you very much, Mr. Chairman.

The issue of autism has been getting increased attention in Congress over the last several years, and this attention is overdue. I want to commend you, Mr. Burton, for your efforts to increase public awareness about autism through these hearings.

Autism is a particularly frustrating disease. We still do not understand what causes it and we still do not have a cure. All we know for sure is that its impact on families can be devastating.

During the hearings held in this committee, we have heard parents tell tragic stories of children who appear to be developing normally and then all of a sudden retreat into themselves, stop communicating, and develop autistic behavior. Other parents have testified that their children never start to develop language skills, and instead early on manifest symptoms of autism.

I can only imagine how frustrating and difficult this must be for families. And I appreciate how urgently we need to understand what causes autism, how to treat it, and if possible, how to prevent it.

Fortunately, Congress is beginning to respond. Last year, I cosponsored a bill to increase NIH's funding for autism research. This funding was authorized as part of the Child Health Act, which I also supported.

This year, Congress' challenge will be to appropriate the funding authorized by the Child Health Act. We will not make real progress until we make sure NIH has the funding it needs to research this debilitating disease.

At our first hearing last year, we heard moving statements from the chairman and several witnesses that they had firsthand experience with observing signs of autism shortly after children received the MMR vaccine. These witnesses voiced their suspicion that autism was caused by the vaccine.

I was deeply concerned about these remarks. Vaccines are unique in medicine. Other medicines are administered to sick people to make them better. But vaccines are given to healthy children and they are mandatory in many States. When I heard the chairman's concerns, I was disturbed by the possibility that a vaccine that States mandate could be making healthy children sick.

But at the same time, I was also worried for another very different reason. Vaccines are one of the greatest success stories in modern medicine. Because of vaccines, children no longer suffer brain damage or die from measles or are paralyzed by polio. I realize that publicizing fears that vaccines may cause autism could cause some parents to stop vaccinating their children. And I worry that this could be counterproductive. In the name of protecting our children from autism, we could actually be subjecting them to much greater risks of deadly or debilitating diseases such as measles, rubella, damage affecting developing fetuses or brain damage from meningitis.

The theory that the MMR vaccine may contribute to autism had been carefully reviewed by the British Medical Research Counsel, which found no evidence to support it. However, what we needed, I believe, was more study. That is why I proposed during last year's hearing that Chairman Burton join me in requesting that the Secretary of Health and Human Services convene a panel of experts to examine the theory that the MMR vaccine could cause autism.

HHS responded to our request by contracting with the Institute of Medicine, a branch of the National Academy of Sciences, to convene a panel of independent experts to review vaccine safety issues. The Institute of Medicine identified potential experts and then subjected the experts to strict criteria that excluded anyone who had financial ties to vaccine manufacturers or their parent companies, previous service on the major vaccine advisory committees, and prior expert testimony or publications on issues of vaccine safety.

The first issue this independent panel considered was the relationship between the MMR vaccine and autism. This panel of independent experts convened by the Institute of Medicine issued its report on the MMR vaccine this Monday. The report is careful and analyzes all the scientific information available and it concludes that there is no credible scientific evidence establishing a link between the MMR vaccine and autism.

The Institute of Medicine report is consistent with the findings of the British Medical Research Council. It is also consistent with the conclusions of the World Health Organization, the American Medical Association, and the American Academy of Pediatrics. Taken together, the evidence clearly demonstrates that the MMR vaccine is highly unlikely to be a cause of autism.

The next vaccine issue the Institute of Medicine will examine is whether there have been adverse effects from thimerosal, a mercury-containing vaccine preservative. Because of concerns about mercury in vaccines, FDA has acted to remove thimerosal from the childhood immunization schedule. In fact, the entire vaccine schedule is currently available without thimerosal. From a public health perspective, the remaining issue is whether FDA made the right decision in choosing not to recall the thimerosal-containing vaccines that are still on doctor's shelves.

FDA made the decision not to recall the vaccines because of concerns about a potential vaccine shortage. While there may be a theoretical risk to children from the thimerosal, FDA knew that there is a very real risk to children if there is not enough vaccine available to protect them adequately from dangerous diseases such as whooping cough or diphtheria. Moreover, FDA was also aware that the Centers for Disease Control's surveillance has not shown any relationship between thimerosal and developing mental delays.

Based on these facts, FDA's decision seems right, but I will welcome any further insight that the Institute of Medicine is able to offer.

I sympathize with the parents who have testified at our hearings and who will testify today. I want them to know that I am committed to doing everything Congress can to address the problem of autism. It is clear to me that we need to research aggressively the causes and treatments of autism. Unfortunately, I believe the answers must come from science.

I thank the witnesses for appearing today and I look forward to their testimony.

Mr. BURTON. I thank the gentleman from California.

Mr. Horn, do you have an opening statement?

Mr. Kucinich, do you have an opening statement?

Mr. KUCINICH. Thank you very much, Mr. Chairman, for holding this hearing. And thank you very much, Mr. Waxman, for making it possible for me to be a member of this committee.

I have to say, in having the opportunity to sit through these committee hearings, I am taken with the concern for public health that both of my esteemed colleagues have, Mr. Burton and Mr. Waxman. I cannot say that I have formed any conclusion about this because I think it is important to be open to new evidence.

I do think it would be significant and important at this moment to read from the summary from the Immunization Safety Review from the Institute of Medicine, which says, "The Immunization Safety Review Committee concludes that the evidence favors rejection of a causal relationship at the population level between MMR vaccine and ASD. However, this conclusion does not exclude the possibility that MMR vaccine could contribute to ASD in a small number of children because the epidemiological evidence lacks the precision to assess rare occurrences of a response to MMR vaccine leading to ASD and the proposed biological models linking MMR to ASD, although far from established, are nevertheless not disproved.

Because of the limitations of the evidence, the significant public concern surrounding the issue, the risk of disease outbreaks if immunization rates fall, and the serious of ASD, the committee recommends that continued attention be given to this issue. This committee has provided targeted research and communication recommendations. However, the committee does not recommend a policy review at this time of the licensure of MMR vaccine or of the current schedule and recommendations regarding administration of MMR vaccine."

It seems to me that this summary, which comes from the document that is under discussion, does have an inconclusive nature to it in the overall issue, even if it does not recommend removal of licensure of the vaccine. So in exploring the issue of this hearing, why the increased rates, I think the persistence of our chairman on the issue of autism and holding these hearings to update last year's work is well taken.

Often, hearings such as these raise more questions than they give answers, and a determination for finding answers is an example that researchers need to follow. In order to find more answers, I do not believe we should narrow the scope of the research. Rather, it is my hope that through the testimony of parents, Dr. Wakefield, and others we will be able to gain a broad view of the factors that may cause autism.

A recent report released by the Immunization Safety Review Committee at the Institute of Medicine is important in this regard because, again, I want to state the conclusion of the committee that the evidence favors rejection of a causal link between the MMR vaccine and ASD is not the whole story. Media reports have seemed to focus on the first part of the conclusion.

The second part of the conclusion, which is perhaps equally important, is that there is not enough evidence. The committee also concludes that the epidemiological evidence is lacking in both breadth and precision. That, by definition, means that we need to do more research. It means we need to do more specific research.

And while I would agree with Mr. Waxman that given the benefits of the vaccine, we do not want to be in a position where we take the position for challenging health risks to a broad spectrum of America's children, I believe we also need to look at these increased incidents with a sense of mission to find out exactly what is going on. The conclusion that the review made also notes that biologic models that link the MMR vaccine and ASD are fragmentary. The committee identifies the limitations of the available evidence, which can only mean that it is too soon to narrow our scope of possible answers.

Currently, there is $58 million in autism research funds at NIH. Congress needs to focus on more funding for more research. I would submit, instead of focusing just on the brain as the sole search of autism research, we need to have a more holistic approach and review the entire body system. Indeed, there is some evidence—admittedly, limited—that shows that vaccine may cause a physical reaction in the digestive system that may cause autism.

Also, as I understand it, there is no conclusive research on whether or not autism is caused by genetic factors or environmental factors. We may need to look at food allergies, vitamin deficiencies, and pollutants for their potential role in causing autism. By looking at the entire human body and not just the brain as the subject of research, we may find answers to questions that we, as Members of Congress, the Autism Congressional Caucus, parents, researchers, and others seek.

I look forward to the testimony of the witnesses. I encourage Federal agencies and Congress to acknowledge their testimony and have a broad scope in working to uncover the cause of autism with additional and improved research.

Again, I thank the Chair.

Mr. BURTON. Thank you, Mr. Kucinich.

Ms. Ros-Lehtinen.

Ms. ROS-LEHTINEN. Thank you so much, Mr. Chairman.

I merely wanted to congratulate you once again for your valiant efforts in helping bring this potential connection to light. Perhaps there is a connection between the onset of autism and the vaccinations, perhaps not. But I know it is an important issue for this committee and it is something that should be taken seriously.

I congratulate you for sticking to your commitment on this, in spite of the overwhelming pressure you must be under from the mainstream scientific community to let it go. I know in my community we have many cases of autistic children, children being tracked by the school system in a different manner. Maybe we are just getting better with diagnosis, but it just seems alarming to me, in my area of south Florida, the high number of children with autism.

I think it is an important issue for our committee. I think you have been a valiant leader in this fight. We do need to improve the scientific evidence. We need to fund the research. We need to educate doctors in a better way because many times those symptoms are going by unnoticed and the pediatricians just shrug their shoulders and say, don't worry, this is just a phase that child is going through. So we need to improve funding and we need to improve the education for the medical community as well.

I want to thank you, Mr. Chairman, for being brave enough to stick to your agenda and to keep our committee seriously looking at the connection between vaccination and autism and just raise the awareness on the issue of autism itself. And I congratulate our colleagues, Mr. Smith and Mr. Doyle, for forming this coalition, of which I am proud to be a member and with which I am proud to be associated.

Thank you, Mr. Chairman.

Mr. BURTON. Thank you, Ms. Ros-Lehtinen.

Mr. Clay.

Mr. CLAY. Thank you, Mr. Chairman.

I welcome the opportunity to meet with the committee today. I also welcome the opportunity to meet with my fellow Members of Congress who are co-chairs of the Autism Caucus, Representative Christopher Smith and Representative Michael Doyle. I especially welcome the parents of autistic children who are witnesses. It is noted that all of the parents on the panel are doctors. Additionally, I welcome all other witnesses of panels three and four.

Mr. Chairman, my No. 1 focus while I am in office is children. I am a father, as are you, and I am especially grateful that you extend that parental concern through this committee. Autism is a developmental disorder that appears within the first 3 years of a child's life. The exact causes are unknown. Many scientists who study autism find that it occurs during fetal development, while some speculate that there may be a form or forms of autism that occur in the early years of a child's life.

Some parents and researchers subscribe to the theory that this form of autism may be caused by vaccinations. Presently, no confirmed scientific basis links vaccinations with autism and some of the studies that support some of these theories have been discredited.

These are questions to which we must have answers. I have a 4-month-old son and a 7-year-old daughter. To you parents who are witnesses today, your children could just as well have been my children. This is an area that must be given all the resources and attention necessary to find causes, effects, and solutions.

At this point, Mr. Chairman, I would yield back the balance of my time and ask unanimous consent to enter my statement into the record.

Mr. BURTON. Without objection, your prepared statement will appear in the record.

[The prepared statement of Hon. Wm. Lacy Clay follows:]

OPENING STATEMENT-REP WM Lacy Clay
Full Committee Hearing of the Committee on Government Reform

THANK YOU MR. CHAIRMAN. I WELCOME THE OPPORTUNITY TO MEET WITH THE COMMITTEE TODAY. I ALSO WELCOME THE OPPORTUNITY TO MEET WITH MY FELLOW MEMBERS OF CONGRESS WHO ARE CO-CHAIRS OF THE AUTISM CAUCUS, REP. CHRISTOPHER H. SMITH AND REP MICHAEL F. DOYLE. I ESPECIALLY WELCOME THE PARENTS OF AUTISTIC CHILDREN WHO ARE WITNESSES. IT IS NOTED THAT ALL OF THE PARENTS ON THE PANEL ARE DOCTORS. ADDITIONALLY, I WELCOME ALL OTHER WITNESSES OF PANELS THREE AND FOUR.

MR. CHAIRMAN, MY NUMBER ONE FOCUS WHILE I AM IN OFICE IS CHILDREN. I AM A FATHER AS ARE YOU AND I AM ESPECIALLY GRATEFUL THAT YOU EXTEND THAT PARENTAL CONCERN THROUGH THIS COMMITTEE. AUTISM IS A DEVELOPMENTAL DISORDER THAT APPEARS WITHIN THE FIRST THREE YEARS OF A CHILD'S LIFE. THE EXACT CAUSES ARE UNKNOWN. MANY SCIENTISTS WHO STUDY AUTISM FIND THAT IT OCCURS DURING FETAL DEVELOPMENT WHILE SOME SPECULATE THAT THERE MAY BE A FORM OR FORMS OF AUTISM THAT OCCUR IN THE EARLY YEARS OF A CHILD'S LIFE. SOME PARENTS AND RESEARCHERS

SUBSCRIBE TO THE THEORY THAT THIS FORM OF AUTISM MAY BE CAUSED BY VACCINATIONS. PRESENTLY, NO CONFIRMED SCIENTIFIC BASIS LINKS VACCINATIONS WITH AUTISM AND SOME OF THE STUDIES THAT SUPPORT SOME OF THESE THEORIES HAVE BEEN DISCREDITED.

THESE ARE QUESTIONS TO WHICH WE MUST HAVE ANSWERS. I HAVE A FOUR-MONTH OLD SON AND A SEVEN-YEAR OLD DAUGHTER. TO YOU PARENTS WHO ARE WITNESSES TODAY, YOUR CHILDREN COULD JUST AS WELL HAVE BEEN MY CHILDREN. THIS IS AN AREA THAT MUST BE GIVEN ALL THE RESOURCES AND ATTENTION NECESSARY TO FIND CAUSES, EFFECTS AND SOLUTIONS.

At this point, I ask unanimous consent to enter my statement into the record.

Mr. BURTON. Dr. Weldon.

Mr. WELDON. I just wanted to mention my good friend from Ohio, Mr. Kucinich, said earlier that NIH funding for autism research is at $58 million. I believe that actual figure is substantially below that, more in the range of $15 million. I think there is going to be another hearing to get at that issue, but I just wanted the record to reflect that.

Indeed, that is a big part of our problem. We are not funding enough research in this arena. I thank you for calling this hearing, Mr. Chairman.

Mr. BURTON. Thank you, Dr. Weldon.

Mr. Cummings.

Mr. CUMMINGS. Thank you very much, Mr. Chairman. Thank you for holding this hearing today.

During the 106th Congress, the Government Reform Committee held numerous hearings on vaccine safety and the theories on the correlations between vaccinations and autism. Earlier this week, the Institute of Medicine Committee on Immunization Safety Review released a study that reported "there is little evidence of a causal link between vaccinations and autism."

I agree with Dr. Steven Goodman of the Johns Hopkins University of Medicine—which so happens to be located in my district—who was a member of the IOM panel, when he said that "the risk of not immunizing is much greater than any risk from immunizing."

Vaccinations provide important health protections so that our children will not be at risk for a variety of illnesses and diseases. Without vaccinations, the diseases we are now protected from will return.

I applaud the CDC, the National Institute of Child Health and Human Development, the National Institutes of Health, the Food and Drug Administration, as well as the Kennedy Krieger Institute and the Center for Development and Behavior Learning at the University of Maryland School of Medicine in Baltimore for their continued research in this area.

The causes of autism are unknown. There are some effective treatments for some children, but there is no cure. My heart goes out to parents, grandparents—like you, Mr. Chairman—and families of autistic children. I am convinced that with further research a cause and cure will be found.

I am also concerned that there have been approximately 2,800 cases of autism reported in my home State of Maryland. I am also concerned about the rise in the number of autism cases in California, New Jersey, and other States.

As such, I strongly believe that all theories for the cause of autism must be objectively and thoroughly researched. I echo the sentiments of the ranking member of this committee when he expressed last year in the Los Angeles Times that autism must not alarm the American people and steer them away from vaccinating their children.

I welcome the witnesses here today. I look forward to the testimony.

Thank you very much.

Mr. BURTON. Thank you, Mr. Cummings.

Ms. Davis, do you have a comment?

Ms. Schakowsky.

Mr. BURTON. If not, Congressmen Smith and Doyle, would you come forward, please?

We will start with you, Mr. Smith. We normally swear in our witnesses, but I do not think we need to do it with you, too.

Mr. Smith.

STATEMENTS OF HON. CHRISTOPHER H. SMITH, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF NEW JERSEY; AND HON. MICHAEL F. DOYLE, A REPRESENTATIVE IN CONGRESS FROM THE COMMONWEALTH OF PENNSYLVANIA

Mr. SMITH. Thank you very much, Mr. Chairman.

I thank you and the members of the committee for allowing my good friend and colleague, Mike Doyle, and I to be here on behalf of our Coalition for Autism Research and Education [CARE]. It is currently made up of 115 Members of Congress. It is bipartisan. It was formed recently and we have our first major briefing on Friday. The reason for the Coalition is to try to sensitize Members to the need for more research dollars, more focus on this very, very debilitating and heartbreaking tragedy that has been experienced by increasing numbers of Americans.

I think most of you know that autism is a developmental disorder that has robbed at least 400,000 children of their ability to communicate and interact with their families and loved ones. The disorder, at least the common, prevalent number used, is found in 1 of every 500 people in America, although that number may have to be ratcheted upwards, given some of the more recent evidence that is coming forward.

My interest in autism has been a 21-year interest. I first got involved when the Eden Institute and Dr. Holmes in Princeton, NJ brought me to one of their group homes and showed me the kind of work they were doing. I worked with him and others throughout the years to try to do what we could.

But, frankly, I have been amazed at what has not been done at the Government level through the 1980's and into the 1990's on this affliction, this disorder.

What brought me into it even more so in recent years—in one of my largest towns, Brick Township, I became aware through Bobby and Billy Gallagher, a very devoted husband and wife who have two children with autism. They did their own study, if you will, in Brick Township and found that there was an exorbitant number of cases of children with autism. They became alarmed and brought this information to me. They had the documentation and we spent the better part of 3 hours reviwing it. In subsequent meetings, it went on and on as we renewed it further.

We finally brought the CDC and other Government agencies into Brick. Frankly, I was amazed, shocked, dismayed, and saddened by how little the CDC and some of our great Government organizations knew about autism. It was as if the studies were passive, the information collected was little to nonexistent—and that includes in my own State. This began an effort to try to do more, to try to at least get a handle on the prevalence of autism.

What is happening? Is 1 in 500 real? Is it imaginary? Is it fiction? And as you pointed out, Mr. Chairman, what is the causation? Looking at your witnesses and knowing of your own deep, personal commitment, I want to congratulate you at your dogged determination to get at the reason. Why do we have this terrible disorder seemingly cropping up in larger numbers in our communities, as we saw in my own Brick Township, NJ? What was found—and this was very disconcerting—after a professional study by CDC, was that rather than 1 in 500, the number was 4 per 1,000 in Brick. What are the reasons? Nobody really has any answers. The questions and the answers we have gotten in terms of numbers only bring about more questions about why the prevalence? Why does there seem to be a cluster or why do we have a higher number throughout the country?

Our own Department of Education in New Jersey has seen more cases. Maybe this is just better reporting or maybe we have a problem that is an epidemic that has gone largely unnoticed. In 1991 there were 241 cases. That has grown to an incredible 2,354 cases in 1999, an 876 percent increase. In just 4 years, the number of autistic children aged 6 through 21 has more than doubled. So we have a problem that really begs a significant increase in funding, commitment, and prioritization within our Government.

Last year many of us argued successfully that the amount of money going to the CDC and NIH be increased. We are doing it again this year, making a similar request to the appropriators that more money for prevalence and other studies be forthcoming.

Finally, Mr. Chairman, last year we did get a breakthrough with the Centers of Excellence in Autism Epidemiology that was contained in Public Law 106–310. I had introduced legislation that had that in it. We worked with a number of organizations and individuals. Mike Bilirakis, our good friend who chairs the committee, put it as title one of his child health initiative bill. Now that is awaiting full implementation so we can get a better handle on autism with these new centers of excellence looking at prevalence and other issues associated with it.

Again, I want to thank you for your leadership. Let me offer one note of caution. I know the IOM study suggests that there is not a link. And I know that one of their witnesses will be here today to amplify that. But I chair the Veterans Affairs Committee. I remember when the very first amendment I offered dealt with the Agent Orange issue. Tom Daschle, now the minority leader over on the Senate side, and I offered an amendment to try to provide service-connection disability and enhanced medical care for our veterans who had been exposed to dioxin, the contaminant contained in Agent Orange.

For years, what we thought was credible evidence was laid aside and they said there was no link, there is no link, there is no link. Finally, in the latter part of the 1980's, the evidence became so compelling that at least three anomalies associated with that contamination were finally deemed service-connected and were deemed worthy of compensation.

My hope is that this report not end the issue, but only lead to more studies to find out what that causation really is, because we really do not know. Again, it is encouraging. I am a great fan and believer in immunizations. For the record, back in the early 1980's, as a member of the International Relations Committee—and you remember this well, Mr. Chairman—I offered the amendment to create the Child Survival Fund and put $50 million in it. Now it has grown to over $200 million to immunize the world's children against pertussis, measles, tetanus, and other debilitating diseases.

So I am a great believer that immunizations save lives. But if there is a problem, we need to be candid enough, aggressive enough, and honest enough, for the sake of our kids, to go at this and find out what is the causation. God willing, there is no connection. But we need to pursue that aggressively.

Thank you.

[The prepared statement of Hon. Christopher H. Smith follows:]

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Testimony of Congressman Christopher H. Smith (NJ-04)

before the Government Reform and Oversight Committee

April 25, 2001

"Autism: Status Report and Future Opportunities"

Mr. Chairman, thank you for providing us with the opportunity to discuss the status of autism research in America today. I am here in my capacity as the Co-Chairman of the Coalition for Autism Research and Education (C.A.R.E.), which currently has 114 Members of Congress. C.A.R.E. is a bipartisan Congressional Member Organization (CMO) dedicated to improving research, education, and support services for persons with autism spectrum disorders.

Most of us may know that autism is a developmental disorder that has robbed at least 400,000 children of their ability to communicate and interact with their families and loved ones. The disorder affects at least one in every 500 children in America, and much of the recent anecdotal evidence suggests that autism rates are increasing. The real prevalence rate may be closer to one in every 200 children.

In fact, we may be in the midst of a silent epidemic, and not even know it. In a landmark federal study conducted in Brick Township, the third largest town in my district, the Centers for Disease Control and Prevention (CDC) discovered that we had a classic autism rate of 4 children per 1000. For autism spectrum disorders, it was 6.7 children per 1000. Because there are no national autism rates against which we can compare the numbers in Brick, we have no way to know whether Brick's autism rates are too high, too low, or about right.

There is a growing consensus among autism experts that the number of reported autism cases is increasing rapidly. For instance, the New Jersey Department of Education has said that the number of kids classified as autistic in our school systems have increased from 241 in 1991 to an incredible 2,354 in 1999. That is an 876 percent increase! In just four years, the number of autistic children age six through twenty one has more than doubled.

In order to unlock the mysteries of autism, the members of C.A.R.E. are working to increase funding levels for programs focusing on autism spectrum disorders so that our nation can pursue several scientific opportunities that are emerging. Clearly, increased appropriations at the National Institutes of Health (NIH) and the Centers for Disease Control and Prevention (CDC) is a necessary component of an effective strategy to respond to the autism challenge.

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Another important element in fighting autism is this Committee and its oversight over the NIH's implementation of the additional "Centers of Excellence" specified in the Children's Health Act (P.L. 106-310), and execution of the award training and education grants to professionals who provide care for patients with autism, which was also authorized by the Children's Health Act. I strongly urge this Committee to work closely with the NIH so that implementation of P.L. 106-310 is swift, enthusiastic, and effective.

The implementation of the "Centers of Excellence in Autism Epidemiology" specified in P.L. 106-310 is another critical issue of concern. The epidemiology research initiative in P.L. 106-310 was incorporated from HR 274, legislation I introduced, during the 106th Congress. As the author of these provisions, I am particularly eager to see them carried out.

Mr. Chairman, this Committee has an important responsibility to keep in close contact with CDC to make sure they are awarding grants and assistance to states which want to establish their own autism surveillance programs in a timely fashion. CDC has indicated that they must collect data from approximately 30 states before it can move forward with a comprehensive analysis of trends that may reveal correlative factors, potential causes, and hopefully effective treatments and cures for autism.

Without adequate prevalence and incidence statistics, school districts will have a much more difficult time adequately planning for the educational needs of autistic children in their community. The cost of special education programs for school-aged children with autism is often more than $30,000 per individual per year, and the cost nationally for caring for persons affected by autism is estimated at more than $13 billion per year. If a school district mistakenly budgets for five autistic children, and 25 walk through their doors, their entire school budget could be blown off the hinges. Even with the improvements in federal funding for the Individuals with Disabilities Education Act (IDEA) that we're seeking, our school districts desperately need good, population based, autism surveillance programs.

As a co-chairman of C.A.R.E., I am in the process of drafting legislation to take us to the next stage beyond P.L. 106-310. The first phase of our attack on autism was to focus on surveillance, and on the biology of the disorder. The second phase, and the focus of the new legislation, must and will focus on improving education and support services for persons with the autism spectrum disorder.

Right now, there is a critical shortage of qualified and trained education professionals that can appropriately teach children with autism. Many special education programs in the country do not have courses designed specifically to teach autistic children. As a result, when special education teachers are hired by school districts to help disabled children, they often lack the basic skills and understanding to appropriately assist autistic children. Autistic children are not like mentally retarded children, which is why it is very difficult to measure IQ in autistic persons. In some IQ dimensions – namely those relying communications skills – autistic persons often score very low. But in other components of the IQ test, autistic persons can score very high. Unless a special education teacher knows which areas are which, effective instruction is made more difficult, and the autistic child will not develop to his or her full God-given potential.

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C.A.R.E. has been involved in other autism initiatives as well. On April 16, my friend Congressman Doyle and I introduced H.Con.Res. 91, which calls upon Congress to support April as Autism Awareness Month and April 27 as Autism Awareness Day. The resolution also commends the parents and relatives of autistic children for their sacrifice and dedication in providing for the special needs of their autistic children. In addition, H.Con.Res. 91 endorses the goals of increasing federal funding for aggressive research to learn the root causes of autism. Furthermore, my legislation urges the Department of Health and Human Services (HHS) to continue to press for the swift and full implementation of the Children's Health Act of 2000 (P.L. 106-310).

Finally, I want to encourage everyone in this room to attend the first C.A.R.E. briefing on Friday, April 27, at 10 A.M. in 334 Cannon House Office Building. The briefing will focus on the importance of early identification of autism as well as the need for early intervention for children who have been diagnosed with the disorder. The second annual Autism Rally will follow the C.A.R.E. briefing on the Capitol steps at noon.

Again, thank you for providing me with an opportunity to testify today.

Mr. BURTON. Thank you, Mr. Smith.

Mr. Doyle.

Mr. DOYLE. Thank you.

Chairman Burton and members of the committee, I thank you very much for inviting me to speak with you regarding autism and the goals and expectations for the Coalition for Autism Research and Education [CARE].

I want to personally thank you for your interest in expanding our knowledge of autism and autism spectrum disorders and increasing research funding as well as for your members in CARE. Your leadership has brought desperately needed attention to a major children's public health issue that has been neglected for the past 50 years.

As you know, autism is a life-long disorder that significantly impacts the lives of those affected with the disorder as well as the lives of parents and relatives. I need not tell you, Mr. Chairman, of the profound effects autism has on parents and loved ones who provide care for every 1 of these 1.7 million individuals. Autism changes lives forever.

Based on the latest evidence, we can safely say that autism and autism spectrum disorders are now at an epidemic level here in the United States with over 1.7 million individuals affected. That is 1 out of every 150 to 170 children born.

During my tenure as Congressman, I have had numerous meetings with concerned parents, researchers, and advocates who are struggling to get autism research and treatment issues to the forefront of lawmakers' minds. The vast majority are frustrated by the lack of research and essential treatment and services for their children. It is because of them, Mr. Chairman, that I became committed to forming a congressional organization for autism advocacy, along with my good friend, Chris Smith, who I knew already had a strong interest in autism from his work on the ASSURE Act last session, and the Coalition for Autism Research and Education was born.

With CARE, our major goals are to ensure substantial increase in research funding while ensuring that families receive the highest quality treatment possible in accordance with today's knowledge. If we accomplish these goals, the number of children born with autism can be substantially reduced and the revolution biologic treatments of the future can be achieved for those who already have autism.

I join you in your grave concern of an autism-vaccine link and feel strongly that we must examine what vaccines may be doing to our children and thoroughly investigate the late onset autism-measles vaccine connection. Identifying a vaccine-autism link will help countless individuals who develop autism after a vaccination, but we need to fully explore all possible avenues to help those who develop the disorder by some other means.

In my view, we must learn to identify the genetic and biologic basis of susceptibility to vaccine complications so that children at risk can be identified and their vaccinations delayed, while children not at risk can continue to receive vaccinations and the protection from brain injury and death that they provide. In addition, identifying the causes of autism will not cure the 1.7 million individuals who already have ASD. Research must also strive toward the revolutionary biologic treatments of the future so that there is hope for these children and adults. The decoding of the human genome opens the door for the development of cures for autism in the lifetime of children born with autism today.

The bottom line is that we need a lot more funding for autism research. The opinions and testimony this committee will hear are proof of that. I am concerned that if we focus the lion's share of funding on one suspected cause of autism that we could unintentionally pass up vital advances in other areas. I want to provide a lion's share of the funding for research into both the treatments and causes of the disorder equally for the sake of all 1.7 million individuals and families that are now living with the disorder, many of whom were born prior to the introduction of vaccines.

Autism lasts a lifetime and often children with disorders outlive their parents. We need to care for and educate autistic children and adults, provide properly trained staff and educators to meet the highly complex and specialized needs of these individuals. All of this can become very costly over the lifetime of an individual with autism. Steps must be taken to reduce the disability associated with autism so that more and more individuals can work and live semi-independently.

In my home State of Pennsylvania, the Autism Society of America estimates that we have 73,686 individuals with autism. Autism costs Pennsylvania an average of $50,000 per person per year. It makes good sense to invest in research now so that we can get quality services to families and realize the ultimate payoffs of prevention of this disorder in the future and cures for those children and adults who already have autism.

Continued funding of NICHD's 4-year-old Genetics and Neurobiology Network must be maintained if we are to achieve this goal. Combined with the creation and funding of at least five new centers of excellence and three epidemiologic centers, autism research in America can reach new heights and achieve new breakthroughs for autism. Congress must continue to fund existing autism research programs without taking away the much needed funding for them to pay for new ones. I believe that any expansion of research programs must come with a corresponding expansion of funding dollars.

In closing, Mr. Chairman, in western Pennsylvania, we are fortunate to have one of NICHD's collaborative programs of excellence at the University of Pittsburgh. This 4-year-old program is not only making a substantive contribution to the understanding of neurobiology and genetics of autism, it is providing guidance to State legislators in developing surveillance and treatment centers in our State.

I would like to extend a personal invitation to you, Mr. Chairman, and to each member of this committee to come and tour this facility, as I have, meet the researchers and staff, and speak to individuals with autism and parents about their struggles and needs.

Mr. Chairman, I thank you for holding this hearing today and for the opportunity to testify this morning.

[The prepared statement of Hon. Michael F. Doyle follows:]

TESTIMONY OF THE HONORABLE MIKE DOYLE
Remarks to the
COMMITTEE ON GOVERNMENT REFORM
Hearing on
"Autism - Why the Increased Rates? A One Year Update"

Chairman Burton, Ranking Member Waxman, and members of the Committee, I thank you very much for inviting me to speak with you regarding autism and the goals and expectations we hope to realize through the Coalition for Autism Research and Education known as CARE. The Coalition's major goals are to ensure a substantial increase in research funding, while ensuring that families receive the highest quality treatments possible in accordance with today's knowledge.

Mr. Chairman, and Ranking Member, I want to personally thank you both for your interest in expanding our knowledge of autism and autism spectrum disorders and increasing research funding. Your leadership has brought desperately needed attention to a major children's public health issue that has been neglected for the past 50 years.

As you know, autism is a life-long disorder that significantly impacts the lives of those affected with the disorder as well as the lives of parents and relatives. Autism deprives children of their ability to interact with others in ordinary ways, robs them of the means to understand and communicate, and destroys normal reasoning skills.

As this Committee noted last year, the prevalence of this disorder has been increasing globally at an exponential rate. Based on the latest evidence, we can safely say that autism and autism spectrum disorders are now at an epidemic level here in the United States, with over 1.7 million affected individuals. That is 1 out of every 150[1] to 170[2] children born has an autism spectrum disorder. These figures are even higher than the 1 in 500 proposed a few years ago. I need not tell you, Mr. Chairman, of the profound effects autism has on parents and loved ones who provide care for every one of these 1.7 million individuals. Autism changes lives forever.

The impact of autism on families was first brought to my attention years ago during my tenure as Chief of Staff for a Pennsylvania state senator. I met a man by the name of Dan Torisky, who today I have the honor of calling a friend and constituent. Dan's son Eddie has moderately severe autism. From the first day we met, I was struck by the tenacity and commitment of Dan and his late wife Connie as they worked tirelessly to make the most normal life possible for their son. I was also struck by the enormity of this effort and the few resources available to them. The Toriskys gave me my first comprehensive lesson on what it meant for a family to live with autism.

During my tenure as Congressman, I've had numerous meetings with concerned parents, researchers, and advocates who are struggling to get autism research and treatment issues to the forefront of lawmakers minds. From those various meetings, one aspect stands out above all others. I am very impressed with the dedication and commitment families have displayed. The vast majority are frustrated by the lack of research and of essential treatment and services for their children. It is because of them, Mr. Chairman, that I became committed to forming a Congressional organization for autism advocacy.

I enlisted the help of a good friend, Chris Smith, who I knew already had a strong interest in autism from his work on the ASSURE act last session, and the Coalition for Autism Research and Education was born. And I'd like to note, Mr. Chairman, that you were among the very first to join this Caucus on the day we officially chartered it, and I would like to thank you for your support. By pooling our strengths, views, and resources, CARE can be a definitive and bipartisan force for autism in congress and a resource to lawmakers, and most importantly, parents and families.

Although your Committee has been ahead of the curve when it comes to examining federal research activities in autism, in general, Congress has not paid sufficient attention to this disorder, as has the National Institute of Health. I strongly believe that now is the time for all of us to come together and combine our unique perspectives, knowledge, and energies to focus on achieving wide-spread availability of high quality treatment and services to families and on substantially increasing research in autism. If we accomplish these goals, the number of children born with autism can be substantially reduced and the revolutionary biologic treatments of the future can be achieved for those who already have autism.

Recently, CARE has introduced legislation, H.Con.Res. 91, that supports the goal of increasing Federal funding for aggressive research into the root causes of autism and its treatment, and urges the swift and full implementation of the Children's Health Act of 2000. Additionally, we are circulating a letter requesting appropriations for at least five new NIH centers of excellence and three CDC epidemiologic centers specified in this Act, and for continuing the recently funded NICHD network of 10 Collaborative Programs of Excellence in Autism (CPEAs). Using the CARE group as a forum, we intend to bring researchers, parents and other concerned individuals to Capitol Hill so lawmakers can hear their stories and become more informed about autism. These are just a few of the activities we are pursuing with CARE.

[1] Center for Disease Control report on the "Prevalence of Autism in Brick Township, 1998" reported 1:250 children have autism and 1:150 have ASD (Autism, Asperger's Disorder, and Pervasive Developmental Disorder Not Otherwise Specified).

[2] Baird et al., "A Screening Instrument for Autism at 18 months of Age: A 6-year Follow-Up Study. J. Am. Acad. Child Adolesc. Psychiatry, 39:6, June 2000 reported 1:325 children have autism and 1:170 have autism spectrum disorder.

This Committee has led the charge in investigating the autism-vaccine link and I join you in your grave concern with this issue and feel strongly that we must examine what vaccines may be doing to our children and thoroughly investigate the late-onset autism/measles vaccine connection. But, Mr. Speaker, such etiologies may take a considerable amount of time to define and past research indicates that it is likely that there is more than one cause of autism. Identifying a vaccine-autism link will help countless individuals who developed autism after a vaccination, but we need to thoroughly explore all possible avenues to help those who developed the disorder by some other means.

In my view, we must learn to identify the genetic and biologic basis of susceptibility to vaccine complications, so that children at risk can be identified and their vaccinations delayed, while children not at risk can continue to receive vaccinations and the protection from brain injury and death that these provide. In addition, identifying the causes of autism will not cure the 1.7 million individuals who already have autism spectrum disorder. Research must also strive toward the revolutionary biologic treatments of the future so that there is hope for these children and adults. The decoding of the human genome opens the door for the development of cures for autism in the lifetime of children born with autism today.

The bottom line is that after 50 years of sub-par efforts we need a lot more funding for autism research. I am concerned that if we focus the lion's share of funding on one suspected cause of autism that we could unintentionally pass up vital advances in other areas. I want to avoid a situation like this, and provide adequate funding across the board for all research activities involving autism, for the sake of all the 1.7 individuals and families that are now living with the disorder, many of whom like Eddie Torisky were born prior to the introduction of vaccines.

We also must improve the quality of life for individuals with autism, while not turning our back on quality research into the causes and treatment. Autism lasts a lifetime and often, children with the disorder outlive parents. This creates a burden on health care and social service systems nationwide, one they are ill prepared to carry. Additionally, we need to care for and educate autistic children and adults, provide properly trained staff and educators to meet the highly complex and specialized needs of these individuals. All this can, as you might imagine, become very costly over the lifetime of an individual with autism. Steps must be taken to reduce the disability associated with autism so that more individuals can work and live semi-independently.

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In my home state of Pennsylvania, the Autism Society of America estimates that we have 73,686 individuals with autism, which translates into about .6% of the total population. This is based on current prevalence estimates of 60 individuals with ASD per 10,000 in the Commonwealth have autism spectrum disorder. The costs of caring for and providing services to these individuals per year is astronomical. If you take into account early intervention, special education, wrap around services, transportation to special programs, respite care, housing and special programs for adults with autism, and housing for those semi-independent, over the course of one year, it is estimated that autism costs Pennsylvania an average of $50,000 per person with autism spectrum disorder per year. This works out to $3,711,642,832 per year.

As you can see, the economic impact on families in Pennsylvania is quite significant, but autism has a far greater impact of the emotional and social activities of families in our communities. If the appropriate steps are not taken, these financial and emotional costs are only going to continue to grow.

It makes good sense to invest in research now, so we can get quality services to families now, and realize the ultimate payoffs of prevention of this disorder in the future and cures for those children and adults that already have autism. Continued funding of NICHD's 4 year old Genetics and Neurobiology Network must be maintained if we are to achieve this goal.

Combined with the creation and funding of at least 5 new centers of excellence and 3 epidemiologic centers, autism research in America can reach new heights and achieve new breakthroughs for autism. But only if Congress continues to fund existing autism research programs without taking away much needed funding from them to pay for new ones. I believe that any expansion of research programs must come with a corresponding expansion of funding dollars. In the western Pennsylvania region, we are fortunate enough to have one of NICHD's Collaborative Programs of Excellence at the University of Pittsburgh. This four year old program is not only making substantive contributions to the understanding of the neurobiology and genetics of autism, it is providing guidance to state legislators in developing surveillance and treatment centers in our state.

In closing, Mr. Chairman, I would like to extend a personal invitation to each member of this committee to come and tour this facility, as I have, and meet the researchers and staff, and speak to individuals with autism and parents about their struggles and needs. You will leave in awe of the heroism of the parents, struck by the vulnerability and needs of these individuals, and convinced of the power of science to change the lives of people with autism.

Thank you for you for your time and for the opportunity to testify this morning.

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Mr. BURTON. Thank you, Mr. Doyle.

Let me start with you Representative Smith.

In Brick Township, as I recall—and you may have to refresh my memory—there were some toxic chemicals or something there. What were those chemicals?

Mr. SMITH. We had problems with a number of toxic chemicals. As a matter of fact, we invited the ATSR, the agency that looks for environmental pathways, to come in and they did their own study and ruled out—based on the proximity of where the children with autism lived and whether or not they were close to the river——

Mr. BURTON. What were the chemicals? Do you recall?

Mr. SMITH. PCBs—there were a number of chemicals. It was a witch's brew in essence of chemicals. They did look for a number, and I could provide that for the record.

Mr. BURTON. I would like to have that. Did they find any mercury in there?

Mr. SMITH. I do not believe they did.

Mr. BURTON. But they found PCBs?

Mr. SMITH. Yes, and others. We are a very industrial State in the State of New Jersey. Many of those chemicals were dumped into the river and got into the water system.

But despite concerns about that, when an overlay of where the children were living was done, there seemed to be no causation that could be attributed to an environmental pathway. So they ruled that out.

Mr. BURTON. How many were there?

Mr. SMITH. There were 4 per 1,000.

Mr. BURTON. So 1 in 250.

Mr. SMITH. And 6.7 for the full spectrum.

Mr. BURTON. Representative Doyle, you indicated that there were 170,000 children in Pennsylvania who are autistic?

Mr. DOYLE. Mr. Chairman, 73,686.

Mr. BURTON. And you said that it cost $50,000 a year to take care of those people that are autistic.

I guess the one thing I would like to point out to anyone from CDC or health agencies, or anyone connected with our Government—let's just say we reduce that $50,000 to half and we only had to spend $25,000 per person for the rest of their life to deal with their autistic problems. If 1 in 250 or 1 in 500 people are autistic, you are talking about so much money that we cannot afford it. We are going to have people walking around that are going to be lost and will be causing all kinds of problems for our entire society. It could cause tragic consequences for the entire country.

So there has to be more research done to find the causes and if possible to find ways to minimize the damage done to these people so they can be productive members of society.

I am very happy for both of you being here and for you sponsoring and supporting and starting the Autism Caucus. I am very happy to be a partner with you on that. Anything I can do to help you get more money for this research, just holler. We will be glad to do it.

With that, Mr. Horn.

Mr. Clay.

Doctor.

Ms. Schakowsky.

Any questions for any of our panelists?

If not, thank you both for being here. I look forward to working with both of you. I appreciate it.

Our next panel is Dr. James Bradstreet, who will be introduced by Congressman Weldon; Dr. Cindy Kay Schneider, of Southwest Autism Research Center in Arizona; Dr. Jeff Segal of Greensboro, NC, formerly of Terre Haute, IN; and Dr. Sharon G. Humiston, of Plattsburgh, NY.

Would you all stand, please?

[Witnesses sworn.]

Mr. BURTON. We want to try to confine the remarks. I know you have prepared statements that are much longer than 5 minutes. But if you would, I would like you to stick as close to the 5-minute limit as possible because we have 14 witnesses today and we want to have time for questions.

Let me start with Dr. Bradstreet.

Dr. Weldon, do you want to introduce him?

Mr. WELDON. Yes, thank you, Mr. Chairman.

It is a real pleasure and honor for me to be able to welcome and introduce my good friend and colleague—that is, medical colleague—from the Melbourne-Palm Bay area, Dr. Jeff Bradstreet.

Dr. Bradstreet is well known to the community I live in, both as a practicing family physician and also for a radio program that was carried nationwide, the Good News Doctor. He is a fellow of the American Academy of Family Physicians. With the development of autism in his son, he has emerged as one of the leading practitioners in treatments of autism and currently receives referrals from throughout the country from parents who have been devastated by this disease.

It is a real pleasure for me to be able to welcome you, and I am looking forward to your testimony as well as that of all the other witnesses we have today.

Mr. BURTON. Thank you, Dr. Weldon.

Dr. Bradstreet.

STATEMENTS OF JAMES J. BRADSTREET, M.D. FAAFP; CINDY KAY SCHNEIDER, M.D. FACOG; JEFF SEGAL, M.D.; AND SHARON G. HUMISTON, M.D.

Dr. BRADSTREET. As a minor introduction to myself, I had absolutely no interest in autism until it affected my son, at which time—in a very short amount of time because of a complete lack of local resources—I wound up having to dedicate myself full-time to this activity which, in the end, was apparently a blessing.

[Slide presentation.]

Dr. BRADSTREET. This is just to remind us that we cannot overfocus our attention on just the vaccine issue. There is a host of environmental toxicological issues that may be interacting with the vaccine constituents to cause problems, and this U.S. News article points to that.

I want to point your attention to this, which is from the November 17, 2000 Oregonian. There are now over 3,000 children in Oregon—I am in Florida, but I was lecturing in Oregon and meeting with researchers at the medical school. That makes a prevalence of 1 in 190 students. The national average, actually, based on recent statistics I have been able to acquire from the Internet—the reference of which are all in my written statement—may be as low as 1 in 140. That is an extraordinary prevalence.

I also want to point your attention to the red line, which shows the point in time that we introduce the infant HiB vaccine and shortly after that, the Hepatitis B vaccine to newborns on the first day of life—what happens to the prevalence of that disorder in Oregon during that period of time.

This is from the U.S. Census on Americans with disabilities. The blue arrow is slightly above, but that number is 1.8 percent of children under 3 being labeled as developmentally delayed—which is a synonym for autism, in many cases or certainly autism spectrum disorders.

If you go to the 3 to 5-year-olds, that is 2.7 percent of children that are labelled developmentally delayed by our U.S. Government. I would tell you that is a multi-trillion-dollar problem coming that you are going to have to deal with, and that is a huge prevalence. That is an epidemic by anybody's standards.

This is the British Medical Journal article that is so famous or infamous in terms of supposedly refuting the incidence of autism-MMR relationship. Again, I do not want to over-focus on any one particular vaccine, but look at when the infant HiB was introduced into England with that red arrow and what happened to the incidence at that point in time. Is there an interaction between MMR components and HiB? Is there science behind that? I would tell you that there probably is. This is from the Mayo Clinic. Briefly, this is a 2000 article that came out in the American Journal of Gastroenterology that said that measles virus infection is associated with inflammatory bowel disease. The IOM report states that no cases of vaccine encephalitis have ever been reported, but what about this case that came out in 1999 that says that measles-inclusion encephalitis caused by the vaccine strain of measles was proven using PCR data.

In addition to that, the IOM report also states that MMR may be associated with inflammatory bowel disease, but concludes that it is still safe. This is from the recent Journal of Pediatrics about a month or so ago that shows that there is in fact marked autoimmunity in these children's intestinal tract. This is most likely an autoimmune disorder in general.

This is the parent's view of what it looks like.

That is what for 4 years of my son's life I got to change about three or four times a day and my wife got to change another three or four times a day as he had chronic diarrhea. The parents have a rather dim view of what chronic inflammatory bowel disease and autism look like.

I want to let you know that it can be fixed. This is part of my Christmas card from one parent thanking me for the fact that in fact it is nice to have a child with a well-formed bowel movement. And that child is doing extraordinarily better now that the enterocolitis is taken care of.

Autoimmunity is a process where the immune system gets confused and turned around and thinks that maybe the child is at fault for this.

Myelin, which is the insulator of the brain nervous system, is clearly a problem and there are many things that we are finding in the kids that are abnormal that are affecting melanization. The vaccine constituents may be part of that.

Just briefly, there is a host of credible science that autoimmunity and vaccines are related. We are seeing in our clinic of over 1,000 children in Florida, who come to us from all over the world—in fact, I will be leaving shortly to spend 2 weeks in Indonesia where, after instituting a World Health Organization vaccine program, they went from essentially no autism to an epidemic in Indonesia, as well. I have been hired to go over there for about 2 weeks to work with the government and teach doctors how to take care of this disorder.

I am a clinician and I have to take care of kids. This is a little difficult for you to read, but it is in my report. Let me just state that this is from the Utah State University. This is cerebral spinal fluid of a child who regressed after an MMR vaccine that shows autoantibodies to myelin basic proteins being positive as well as measles virus in the spinal fluid. All other variables were negative.

I would conclude from that—as did the physician and the researchers who have looked at this—that in fact that is an MMR reaction in this child since there was no measles in this child's history.

This just shows that it is not just Dr. Singh at the Utah State University, but myelin basic protein antibodies are prevalent and we can find them at many different laboratories.

We also know that Hepatitis B is an issue, and this shows that as early as 1985 we knew that Hepatitis B constituents had protein peptides that could in fact induce autoimmune encephalitis in rabbits through molecular mimicry. These are the same proteins we are injecting into our children.

We know that the French have identified a problem with demelanization following Hepatitis B vaccine. We see problems with melanization in autism every day in our facility.

This is a quickie just to show you that while there are a lot of different peptides out there, hemophilus peptides do induce autoimmunity to myelin basic protein from the Journal of Immunology in 1999.

Exposure to mercury and other constituents will induce the same autoimmunity to brain elements, and that is a review article that has over 174 references. Is mercury a problem? It is certainly in the vaccines.

This shows just a brief overview of the amount of mercury that is available to children through the vaccines. It is a tragedy. There is a lot of mercury in our environment. It should not have been in the vaccines.

This is my son's first mercury test. That little dot on the fourth column on the left that says toxic elements is in fact a very high level of mercury. That is 15.7 parts per billion, which is extremely high. This is his first post-provocational urine using a standard procedure that has been developed; 24 micrograms per gram in his urine.

This is a New Jersey family—for Mr. Smith. This is a heavy metal study from a child.

This is a 6-year-old with autism.

That is his first post-provocational urine. It shows extraordinarily high levels of lead and mercury. One would conclude that perhaps this is an environmental exposure, so I tested the entire family, trying to be a good doctor.

Look at Mom. Mom is a nurse, Mom has had some vaccines, Mom has a lot of amalgams, but look at that. Mom's mercury is not too bad. Maybe it is not too bad.

Maybe Dad is a battery factory worker—actually, Dad is an engineer, but let us go to Dad. Dad shows very little. He does have some amalgams as well.

How about a 4-year-old sibling that has never been vaccinated that has grown up in the same household. There is essentially no mercury in that child. That causes me, as a physician and as a clinician great concern. In this situation, it looks like heavy metals are a problem. The only place I have to look—the only difference between one child and the other—is vaccination.

Is mercury toxicity a problem in autism? That bottom line on that graph is a mercury level that is so high it could cause neurological developmental disorders. The zinc level is almost at critical levels of deficiency. Those two combinations cause problems.

In summary, TH–1 and TH–2 imbalance where marked TH–2 insult has occurred through the vaccination program is well documented from researchers at the University of California at Irvine. TH–2 causes autoimmunity as vaccine-related. We see it in our kids every day.

That is basically the issue we think that thimerosal plus environmental mercury causes the initial TH–2 skewing and autoimmunity. Aluminum adjuvants, which are in the vaccines, adds to that infant. Infant HiB, again, is a strong TH–2 impulse agent. Newborn Hepatitis B is another TH–2 agent. All these so far have been associated with autoimmune reactions, with the exception of aluminum.

Pertussis is a TH–2 potent stimulator. This is an immune system within the child that is primed to react so that when MMR does come along, we are going to see autoimmune reactions to brain and to bowel. We see it every day. This is an epidemic of neurodevelopmental catastrophe.

This is my son at the Smithsonian. That is what I think autism must feel like to children and to families. That is a T-Rex—big teeth, big problem. But we do know that with love, prayer, and sound medical behavioral action, this does not have to be a catastrophe and there is hope.

The last picture is how Matthew is today. He is a happy well-adjusted child, who is much better.

Thank you.

Mr. BURTON. Dr. Bradstreet, thank you for that very informative testimony. I will have a number of questions for you.

Our next speaker will be Dr. Cindy Kay Schneider of the Southwest Autism Research Center.

Dr. SCHNEIDER. Good morning, Mr. Chairman and members of the committee. My name is Dr. Cindy Schneider.

I would like to express my gratitude and that of the hundreds of families I represent to Representative Burton for his scrutiny of the medical issues related to autism and his leadership in bringing these concerns to your attention.

In 1995, my son Derek and daughter Devon were diagnosed with autism. After visits to several specialists and series of medical tests, we were left with a diagnosis and nothing more. No treatment, no plan of action, and no hope.

The following year, Dr. Ron Melmed, Denise Resnik, and I founded the Southwest Autism Research Center, a nonprofit organization dedicated to serving the needs of individuals with autism. We developed a questionnaire for the purpose of obtaining medical, developmental, behavioral, and family histories. We began to send laboratory specimens to researchers around the world.

This became the infrastructure of a data base which now contains information on approximately 500 children with autistic spectrum disorders, their siblings, and 200 unrelated controls. Many of these children have undergone extensive psychological testing through our center and hundreds have participated in clinical research trials. In this very limited time, I would like to share with you the highlights of our findings.

We looked first at patterns of development; 60 percent of children in our data base spoke their first word prior to 18 months of age, indicating that early language development was usually intact. The majority of children acquired motor skills at the expected age as well.

Because my children experienced a distinct loss of language and deterioration in health after their first year of life, I looked for this pattern in other children. When asked if their child had a normal or near-normal period of development followed by regression, nearly 80 percent of parents told us yes.

The most frequent age of regression was between 13 and 18 months. Consider the possible explanations for this deterioration. These might include a metabolic defect which over time results in neurological damage in a previously healthy child. Exposure to toxins in the environment could do the same. Infections, either naturally occurring or acquired through vaccination, must also be considered.

For the past 3 years, we have collaborated with researchers in Rome on a genetic screening project. Antonio Persico and Flavio Keller have conducted detailed evaluations of 184 families in Italy and the United States, including 44 of our children at SARC. Investigation of four candidate autism genes revealed that three have little effect on a child's risk of developing autism. The fourth gene is related to reelin, a protein critical in early brain development.

In the Italian population, carrying a variant of this gene more than doubled an individual's probability of having autism. In the American subjects, the risk of autism associated with the inheritance of this allele is 19 times the usual risk; 20 percent of individuals with autistic spectrum disorders carry this gene. The inheritance of the long allele of this gene results in a lower production of reelin. Interestingly, viral infection further reduces reelin production and may explain frequent reports of children's deterioration into autism following illness or vaccination.

Other research at SARC has focused on the health problems associated with autism. Of the 500 families interviewed, 48 percent reported that their children have a history of chronic diarrhea, chronic constipation, or alternating gastrointestinal symptoms. The increased incidence of bowel disease in individuals with autism has been confirmed by multiple investigators over the past 4 decades, yet has been largely dismissed by the physicians caring for these children.

Our interest in the gut-brain connection intensified in 1997 when we learned of several children with autism who experienced remarkable improvement following the administration of a gastrointestinal hormone called secretin.

In 1998, we initiated the first clinical trial of the safety and efficacy of synthetic human secretin in the treatment of autism; 30 children were enrolled in this phase one study. Improvements were noted in language, social awareness and interaction, sleep pattern, and gastrointestinal but were not captured on standardized psychological and language tests. We saw that some children benefited from this treatment, yet the study of this heterogeneous group failed to demonstrate this benefit.

Over the past year, we have collaborated with Repligen Corp. and four other sites across the country in the first phase two clinical trial ever performed in the treatment of autism. There were 126 children who completed this double-blind, placebo-controlled study. Each child received three doses of either synthetic human secretin or placebo at 3-week intervals.

Unlike previous secretin studies, enrollment was restricted to children between the ages of 3 and 6 who met strict inclusion criteria. These criteria included a diagnosis of childhood autism, a moderate to severe level of impairment, little or no language, and significant gastrointestinal symptoms. In addition to formal psychological testing, we asked parents to report their children's status at the completion of the study using a clinical global impression scale.

Treatment with three doses of secretin produced a significant decrease in the symptoms of autism in 42 percent of children, while 27 percent in the placebo group improved. Further data analysis is underway and will take several months to complete, but early findings indicate a biochemical market which may predict secretin response.

Additional research planned at the Southwest Autism Research Center includes expansion of our current data base through recruitment of additional families and extensive medical and behavioral assessments of these children. Genetic testing for candidate autism genes and screening for several metabolic defects will be performed.

An associated research priority will be the establishment of a sibling screening clinic in which younger siblings of children diagnosed with autism will undergo the same testing. The recurrence rate of autism is approximately 5 percent, meaning that parents of a child with autism have a 5 percent change of having another affected child. Siblings age zero to 3, the age of onset for autism, will be evaluated every 3 to 6 months. In this way, identification of risk factors will facilitate diagnosis and treatment at the earliest possible age. This program will also allow prospective data collection related to the natural history of autism, its associated biochemical distinction, and the role of suspected environmental variables.

The establishment of these programs on a national level could allow the genetic environmental variables responsible for the development of autism to be identified in the foreseeable future.

I thank you for your attention to this subject and look forward to participating in the materialization of this vision.

[The prepared statement of Dr. Schneider follows:]

Cindy Kay Schneider, MD, FACOG
Medical Director
Southwest Autism Research Center
Testimony to Government Reform Committee
April 25, 2001

Good morning Mr. Chairman and Members of the Committee,

My name is Dr. Cindy Schneider. Thank you for the opportunity to discuss a public health crisis we face as a nation today. I'd like to express my gratitude and that of the hundreds of families I represent to Representative Burton for his scrutiny of the medical issues related to autism and his leadership in bringing these concerns to your attention.

In 1995, my son Derek and daughter Devon were diagnosed with autism. They were 2½ and 3½ years of age at the time. After visits to several specialists and a series of medical tests, we were left with a diagnosis and nothing more. No treatment, no plan of action, no hope. I was told then that the incidence of autism was 4 per 10,000. It is now conservatively estimated to affect 1 in 500 children.

When investigating the research being done related to autism, I found that the primary focus was on genetics. We agreed to participate in some of these studies, but were dismayed to learn that information from one group was seldom shared with other researchers. We were expected to have blood drawn from every family member again, to undergo the same psychological testing again, and to spend hours in interviews rather than transferring the appropriate data and genetic material from one university to another. It became clear to me that not only was more research needed, it could certainly be conducted in a better way.

In 1996, Dr. Raun Melmed, Denise Resnik and I founded the Southwest Autism Research Center, a nonprofit organization dedicated to serving the unmet needs of individuals with autism. We developed a questionnaire for the purpose of obtaining medical, developmental, behavioral, and family histories. We began to send laboratory specimens to researchers around the world. This became the infrastructure of a database which now contains information on approximately 500 children with autism, their siblings, and 200 unrelated controls. Many of these children have undergone extensive psychological testing through our center, and hundreds have participated in clinical research trials. In this very limited time, I would like to share with you the highlights of our findings.

We looked first at patterns of development. Sixty percent of the 500 children in our database spoke their first word prior to 18 months of age, indicating that early language development was usually intact. The majority of children acquired motor skills at the expected age as well.

Because my children experienced a distinct loss of language and deterioration in health after their first year of life, I looked for this pattern in other children. When asked if their child had a normal or near-normal period of development followed by regression, nearly 80% of parents said "yes". The most frequent age of regression was between 13 and 18 months. Consider the possible explanations for this deterioration. These might include a metabolic defect present from birth, producing a toxic product of metabolism. Over time, this metabolite could theoretically result in neurological damage in a previously healthy child. Exposure to toxins in the

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environment could do the same. Infections, either naturally occurring or acquired through vaccination, must also be considered.

We looked next at research being done around the world. Paul Shattock in England was studying a compound called indolyl acriloyl glycine, or IAG. IAG is found at low levels in most individuals, but is seen at high levels only in children with autism, their immediate family members, and in military personnel suffering from Gulf War syndrome. In our own population, we found that 68% of the children with autistic spectrum disorders had elevated levels of IAG. Seventy-three percent of their unaffected siblings did as well.

Another area we've been studying since 1996 is Karl Reichelt's work at the University of Oslo related to urinary peptides. He and others have found that protein fragments believed to originate from milk and gluten-containing grains are found at high levels in the urine of individuals with autism. As with IAG, we found that children with autism and their siblings had distinctly elevated peptide levels as compared to typically developing unrelated controls. It appeared to us that those with high peptide levels were often more severely impaired than were children with lower peptide levels. This was confirmed by standardized psychological testing including the Childhood Autism Rating Scale, the Guilliam Autism Rating Scale, and the Vineland Adaptive Behavior Scales. It has been our observation that those children with elevated urinary peptide levels often improve dramatically when milk and wheat are removed from their diet, and this improvement is associated with a decrease in their urinary peptide levels. This intervention is viewed with skepticism in the general medical community, yet we have only to consider PKU, diabetes, or gout in recognizing the impact that diet may have in the balance between disease and health.

Our international collaboration expanded to include genetic screening through Libera Universita Campus Bio-Medico in Rome. Antonio Persico and Flavio Keller have conducted detailed evaluations of 44 of our families at SARC and 91 families in Italy. Investigation of four candidate autism genes revealed that three, including the serotonin transporter gene, have little effect on a child's risk of developing autism. The fourth gene studied is related to reelin, a protein critical in early brain development. In their Italian population, carrying a variant of this gene more than doubled an individual's probability of having autism. In the American subjects, the risk of autism associated with the inheritance of this allele is 19 times the usual risk. Twenty percent of individuals with autistic spectrum disorders carry this gene, indicating that it is a risk factor for 1 patient in every 5. The inheritance of the long allele of this gene results in a lower production of reelin. Interestingly, viral infection further reduces reelin production, and may explain frequent reports of children's deterioration into autism following illness or vaccination.

Other research at SARC has focused on the health problems associated with autism. Of the 500 families interviewed, 48% reported that their children have a history of either chronic diarrhea, chronic constipation, or alternating gastrointestinal symptoms. The increased incidence of gastrointestinal disease in individuals with autism has been confirmed by multiple investigators over the past four decades, yet has been largely dismissed by the physicians caring for these children. Torrente, Machado, Wakefield, and others at the Royal Free and University College Medical School investigated these gastrointestinal symptoms in 25 children with regressive autism and found it to be an autoimmune disease. Each of the 25 children had the inflammatory bowel condition now known as autistic enterocolitis, and Dr. Wakefield will describe to you this disease and its implications. Recognize that these findings could well apply to nearly half of all children with autism.

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Our interest in the gut-brain connection intensified in 1997, when we learned about the experience of a little boy named Parker Beck. Parker is a child who developed a regressive form of autism which was associated with severe diarrhea. He was evaluated by Dr. Karoly Horvath at the University of Maryland, and underwent a test of pancreatic function known as a secretin challenge test. During this procedure, a dose of the gastrointestinal hormone secretin was infused intravenously. Not only did he have an exaggerated pancreatic response to this infusion, within three weeks of this procedure, his diarrhea of two years' duration resolved. This resolution of his bowel disease was associated with a profound improvement in his symptoms of autism. Although previously nonverbal, he acquired hundreds of words in a matter of weeks. Like many children with autism, he suffered from a significant sleep disorder, but this too resolved. He began to interact with his sister and other children for the first time.

In 1998, the Southwest Autism Research Center initiated the first clinical trial of the safety and efficacy of synthetic human secretin in the treatment of autism. Thirty children between the ages of 2 and 10 were enrolled in this Phase I FDA study in which two thirds received secretin, and one third was given placebo. Improvements were reported and observed in language, eye contact, social awareness and interaction, mood, activity level, sleep pattern, and gastrointestinal symptoms. Unfortunately, there was no distinction between treatment and placebo groups as measured by standardized psychological and language tests. We recognized that some children benefited from this treatment, yet the study of this heterogeneous group failed to demonstrate this benefit. We reviewed our limited data and that from other similar studies in an attempt to identify predictors of secretin response. Variables considered included the severity of impairment, the presence or absence of gastrointestinal symptoms, age of onset of autism, gender, diet, and concurrent medications.

Over the past year we have collaborated with four other sites across the country in the first Phase II FDA clinical trial ever performed in the treatment of autism. One hundred and twenty-six children completed this double-blind, placebo-controlled study. Each child received three doses of either Repligen synthetic human secretin or placebo at three-week intervals. Extensive medical and psychological testing was performed on all children. Unlike previous secretin studies, enrollment was restricted to children between the ages of three and six who met strict inclusion criteria. These criteria included a diagnosis of childhood autism, a moderate to severe level of impairment, little or no language, and significant gastrointestinal symptomatology. No children with seizure disorders or concomitant use of psychotropic medications were enrolled. In addition to formal psychological testing, we asked parents to report their children's status at completion of the study using a Clinical Global Impression scale. A score of 4 on this scale would indicate no change over the course of the study, while a score of 7 would be given to a child with very significant deterioration and a score of 1 would indicate very significant improvement. Treatment with three doses of secretin produced a significant decrease in the symptoms of autism in 42% of children in the treatment group as measured by the parental Clinical Global Impression scale, with a p value of 0.02. The same trend was noted in the psychologists' Clinical Global Impression scale, but the p value did not reach statistical significance. Likewise, significant improvement in symptoms as measured by the Child Autism Rating Scale occurred in 17 of the 126 children in this study, 12 of whom received secretin. These scores did not reach statistical significance, but reflect an encouraging trend toward greater improvement in a select group of children. Further data analysis is underway, and will take several months to complete. Early findings indicate a biochemical marker which may predict secretin response. Fifty-two percent of children with a specific biochemical profile received a parental Clinical Global Impression score of 1 or 2, indicating that they were much improved or very much improved at the time of study completion.

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Brief episodes of flushing and increased heart rate appear to be secretin-related side effects, but no other adverse events were observed in treatment over placebo groups. Children whose families elect to continue in this study will be offered six additional doses of synthetic human secretin this summer in an open-label trial designed to further investigate biomedical indicators of secretin response and the safety of long-term treatment.

Additional research planned at the Southwest Autism Research Center includes expansion of our current database through recruitment of additional families and extensive medical and behavioral assessments of these children. Genetic testing for candidate autism genes and screening for several metabolic defects and autoimmune disease will be performed. An associated research priority will be the establishment of a sibling screening clinic, in which the younger siblings of children diagnosed with autism will undergo medical, developmental, psychological, and laboratory assessments. The recurrence rate of autism is approximately 5%, meaning that parents of a child with autism have a 5% chance of having another affected child. This indicates a 50% increased risk of autism over the background rate. Siblings age 0-3, the age of onset for symptoms of autistic spectrum disorders, will be evaluated every three to six months. In this way, early identification of risk factors will facilitate diagnosis and treatment at the earliest possible age. This program will also allow prospective data collection related to the natural history of autism, it's associated biochemical distinction, and the role of suspected environmental variables.

As the National Institute of Health and Centers for Disease Control contemplate the establishment of Centers of Excellence in autism research, I urge them to consider this model in which a database is created to allow the correlation of laboratory data with clinical presentation. Pairing this with national protocols for sibling screening could allow the genetic and environmental variables responsible for the development of autism to be identified in the foreseeable future. I thank you for your attention to this subject and look forward to participating in the materialization of this vision.

Cindy Schneider, MD
Co-founder and Medical Director
Southwest Autism Research Center

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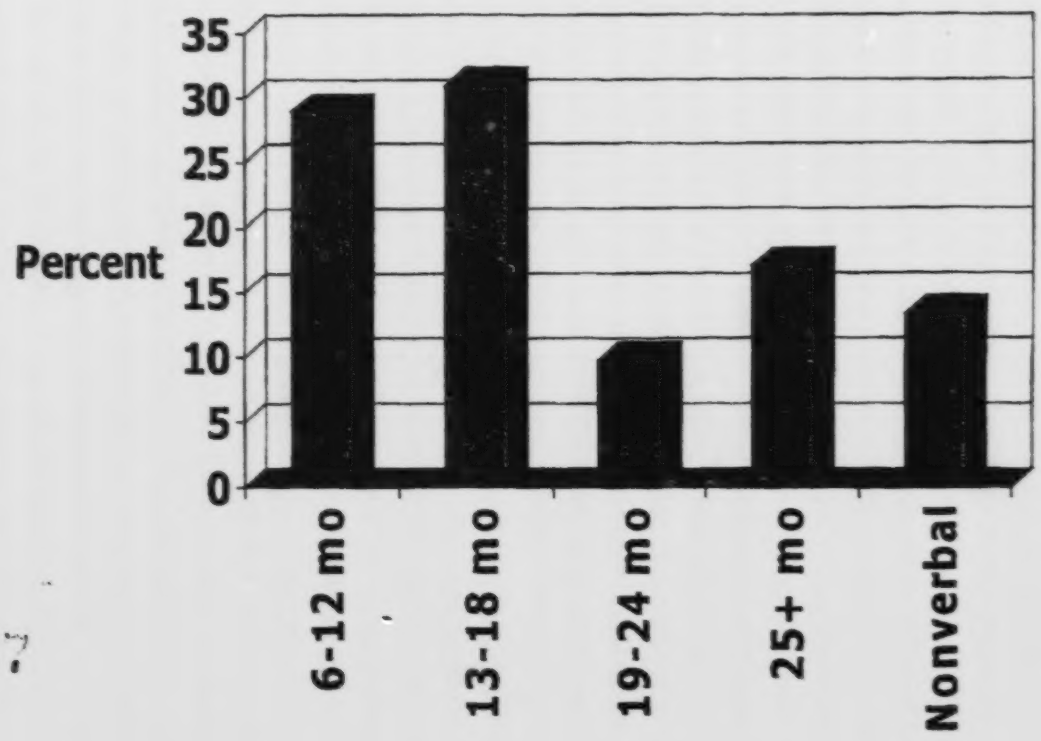
Southwest Autism Research Center

Southwest
Autism Research
Center

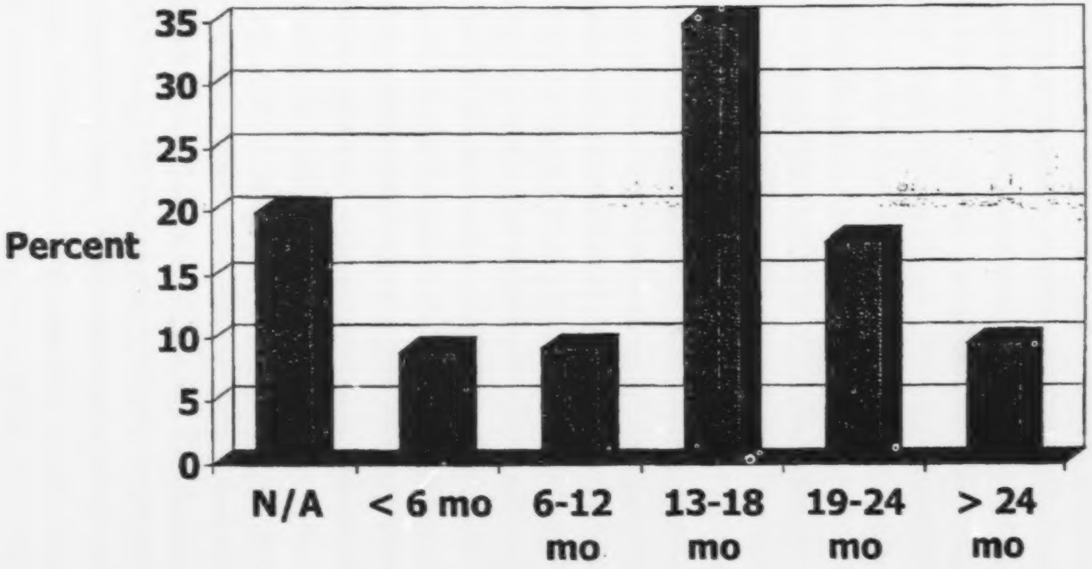
Answering Questions and Questioning Answers

First Word



57

Regression

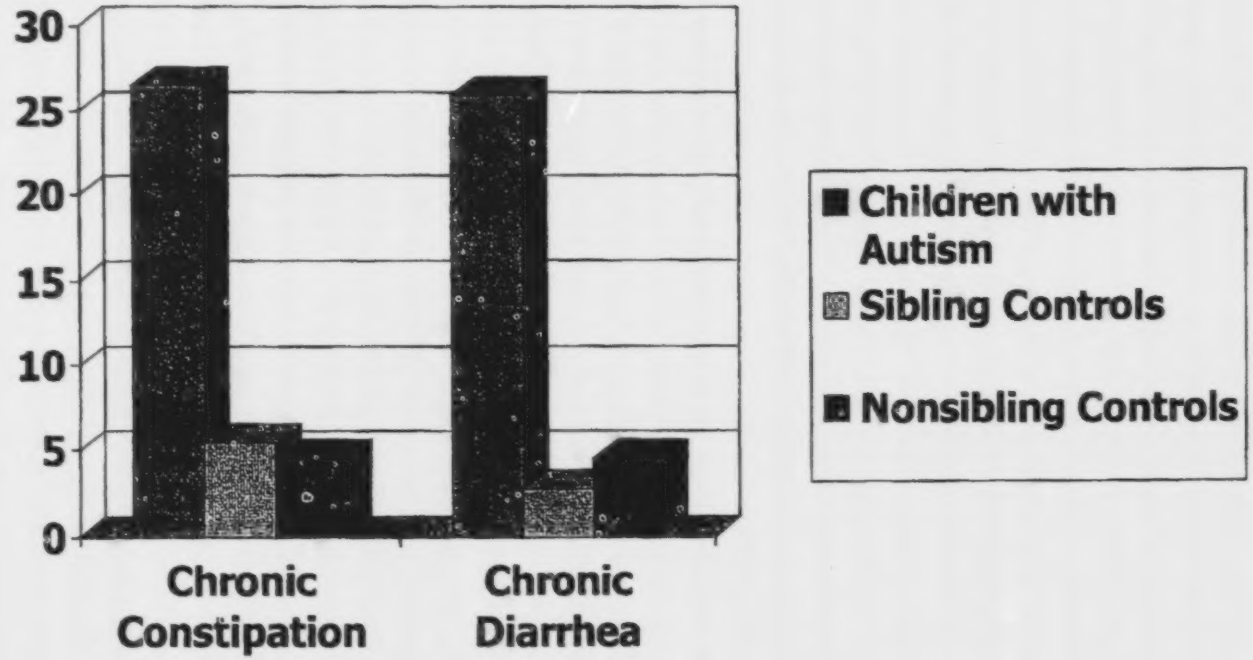


Genetics Screening

Persico et al, Libera Universita di Roma

- Serotonin transporter
- Adenosine deaminase
- Plasminogen activator inhibitor
- Reelin

GI Symptoms


30
25
20
15
10
5
0
Chronic Constipation
Chronic Diarrhea
■ Children with Autism
▨ Sibling Controls
■ Nonsibling Controls

Gastrointestinal Disease

- Asperger 1961: High incidence of celiac disease in autism
- D'Eufemia : Increased permeability
- Wakefield: Autistic enterocolitis
- Horvath: Reflux esophagitis and gastritis
- Torrente & Machado: Autoimmune disease of small intestine in 25/25

Secretin Study Design

- 30 Children with ASD
- Ages 2-10
- 24 boys/6 girls
- Single dose Phase I study

Repligen Secretin Trial

- 126 children at 5 U.S. sites
- Ages 3-6
- 3 infusions at 3 week intervals
- DBPC Phase II trial
- Extensive medical testing

Inclusion Criteria

- Diagnosis of autism
- Moderate to severe impairment
- Little or no language
- Age 3-6
- Gastrointestinal symptoms
- No history of seizures
- No psychotropic medications

Parental Clinical Global Impression

Responder = CGI-P of 1 or 2

	Secretin	Placebo	Difference
All patients	42%	27%	15%
Biomarker Patients	52%	21%	31%

Future Research

- Extension of secretin trial
- Expansion of database
- Genetics research
- Screening for metabolic defects
- Screening for autoimmune disease

Sibling Screening

- Developmental
- Biomedical
- Genetic
- Psychological
- Language

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Autism Research
Center

Answering Questions and Questioning Answers

Mr. BURTON. Thank you, Dr. Schneider, Dr. Bradstreet, and the others.

Do we have copies of your studies? I would like to have as much documentation from all of you as we can get because we are going to have the people from HHS and FDA here. I want to submit your studies to them—along with Dr. Wakefield's and others—and ask them to give us an evaluation of those studies based on their report and their research. In other words, I want to get a comparison.

They are saying one thing and you guys are telling us something else.

Dr. Segal, welcome. It is nice to have a Hoosier here—although we love you guys, too.

Dr. SEGAL. I was born in South Bend, by the way.

Mr. BURTON. Once a Hoosier, always a Hoosier. [Laughter.]

Dr. SEGAL. Mr. Chairman and members of the committee, thank you for the opportunity to speak.

In October 1999, I became a member of a club I never wanted to join. My son was given a diagnosis of regressive autism.

I am the father of 4-year-old twins, a boy, Joshua, and a girl, Jordan. I practiced as a neurosurgeon. My son developed normally and hit all of his milestones. He was jolly, sweet-natured, and very bright. Before his second birthday, he started losing the language he had acquired. He became hyperactive and inattentive to the point that I though he was deaf.

By the time a physician confirmed the diagnosis, my wife, Shelley, and I already knew. We were devastated.

I investigated treatment options. The first treatment consisted of occupational therapy to address his sensory issues. The other early intervention that we chose was called ABA, or applied behavioral analysis. ABA breaks down everyday actions into discrete steps. The training is delivered as one-on-one therapy and involves 40 hours of work a week. It is expensive, exhaustive, and extremely time-consuming. Most families we spoke with were on waiting lists for ABA treatment. As time was our enemy, we moved to North Carolina. I quit my practice and devoted my time to investigating biomedical options.

At this point, I am pursuing three main projects. First, help my son. If I can help him, I can help others. Next, I am researching toxicologic causes and treatments as it relates to autism. I am doing this in concert with the Department of Physiology at Wake Forest School of Medicine. Finally, I am exploring pharmaceutical options. I dug deep into my right pocket and started a drug company based on medications that are likely to be relevant to helping those with autism. At the same time, it turns out it is probably relevant to treating Parkinson's, schizophrenia, and other illnesses.

I have a few observations I would like to make.

The number of children with autism or related disorders is rising. Do not take my word for it and do not ask physicians. We need to ask teachers. These kids are filling regular and special education classrooms to over-capacity.

We have heard the argument that the number of kids with autism is static and that doctors are just better diagnosticians. I have two points. Where are the autistic adults who were never diagnosed 20 years ago? Surely they have to be somewhere. Also, physicians spend less time than ever truly talking with patients and families. More diagnoses are made by tests and machines. No laboratory test exists for autism. The diagnosis is based strictly on clinical examination. Finally, the average time between onset of autistic symptoms and diagnosis is still years. We are not better diagnosticians.

The California Department of Developmental Services is adding one new child with full-blown autism every 3 hours. Estimates vary, but we are looking at approximately $2 million to raise an autistic child to age 21.

The number of physicians who have a deep understanding of autism treatment is small. These doctors are overworked and it takes months to get an appointment. Many of these doctors have affected children of their own. Since autism is a systemic condition that involves that GI tract, immunologic system, and central nervous system, it requires expertise by multiple specialists. Finding all the specialists who have an interest in treating autism can be a daunting task.

The statistics quoted by academicians are at odds with reports by parents. For example, the standard autism literature does not even recognize a general connection with the GI tract and autism. However, families report that up to 80 percent of their children have GI problems. Standard literature suggests that only 20 percent of autistic children regress, that is, they develop normally until age 2 and then become autistic. The majority of parents that we see report that their children fall into the regressive or acquired category.

Andrew Wakefield has theorized about a connection between GI problems and autism. His work suggests that the measles virus from vaccines might persist in GI tissue. This association might also have a causal role in autism. This work urgently needs replication, yet many gastroenterologists conveniently dismiss his work rather than test his theory. Incidentally, it would not be difficult to validate or refute his hypothesis.

Eighty percent of autistic children have abnormal EEG activity in brain areas associated with speech. It is believed that these abnormalities might contribute to language deficits. Correct diagnosis requires at a minimum an overnight EEG. Most kids are given a 1-hour EEG, informed that it is normal, and never properly treated. Not infrequently, the EEG is normal, and a more sensitive test called the MEG is abnormal. MEG is located in only a handful of cities and is quite expensive. Insurance companies do not readily pay for this test. Once correctly diagnosed, children may be given anti-seizure medication, which can help.

Speaking of insurance companies, they do not readily pay for much of anything that is autism-related. Laboratory tests are paid out-of-pocket by parents and most research is being borne at the parent's expense.

ABA treatment is extremely expensive. It works for about half of the children. Costs are approximately $30,000 to $70,000 a year. The parents will frequently turn to school districts to make these treatments available. Where one lives determines the type of treatment one receives. It is not uncommon for the school district to litigate against parents so they will not have to provide that service.

The alternative is placing children in large classrooms. This effectively warehouses the child and minimizes potential for future gain. Waiting lists for services are all too common.

I could spend a lot of time talking about the need for toxins research, but I would like to touch on this for just a second.

The Centers for Disease Control recently reported that 1 in 10 women of childbearing age in the United States are at risk of having newborns with neurological problems due to mercury exposure. Until recently, vaccines had thimerosal as a preservative. Thimerosal is a preservative that contains organic mercury.

Organic mercury is widely recognized as a neurotoxin. In one study, lower or scores neurologic function tests were found years later in children who had been exposed prenatally to intermittent doses of methyl mercury. These doses happened to be from dietary exposure at levels that had been previously thought to be safe.

The vaccine manufacturers, to their credit, have stopped making new vaccines with mercury as a preservative. But many of these vials still sit on doctors' shelves. Also, RhoGAM is given to RH negative mothers and this medication still has thimerosal.

As an anecdote, I spoke with two fertility doctors. They were not aware of the mercury issue. They were livid that this type of medication had a preservative that had "cleared" safety tests and was being given to a pregnant woman.

With more vaccines being recommended to an already-full vaccine schedule, and many vaccines administered earlier in life, the potential for mercury toxicity in children is quite real. The symptoms of mercury poisoning and autism are quite similar.

I recently analyzed 250 hair samples and found that 30 percent of these children had tested two standard deviations above the mean for various metals: aluminum, arsenic, and antimony. These agents are ubiquitous in the environment. It is my belief that autistic children may not be able to clear these toxins from their bodies.

Chelation treatment is one way to remove metal toxins from the body. It uses compounds that have a propensity to grab metal toxins. There are many unanswered questions regarding chelation. I say that historically the reputation for chelation is quite poor. And I say this as a physician who had never previously entertained the idea of chelation for any chronic condition. It is extraordinarily difficult for a practitioner to get funding to study chelation. It is just as difficult to get doctors to consider it as a viable treatment.

My scientific work is focused on analyzing genes and proteins that detoxify heavy metals in autistic children. My hypothesis is that some children are genetically predisposed to the inability to detoxify the metals to which they are exposed to in the environment. These metals may come from vaccines, food, or the environment. The major detox pathway for heavy metals is metallothionein or MT. I am researching whether or not these children have defective MT genes or if they are unable to make appropriate amounts of this protein in response to the insult. This could explain why not all children exposed to the same environmental insult develop autism.

I will close, knowing I am well over the time.

We need immediate and abundant funding for research, particularly treatment. We need to fund fellowships to increase the number of skilled doctors who are treating autism. We need to mainstream autism as it relates to insurance payments. It is a biological condition and should not be constrained by policy limits on mental health coverage.

We need to standardize payments for ABA treatment across the country. It is unfair that some families are on waiting lists for 2 years to access coverage.

We need to get the vials of thimerosal-containing vaccines off the shelves through recall.

Mr. BURTON. Amen.

Dr. SEGAL. We have adequate stocks of vaccine. It is not a problem at this point. We need to clear the shelves. And doctors do not know what is sitting on their shelves. We also need to remove thimerosal from RhoGAM.

We need to seriously test the hypothesis that vaccines are not always as safe as is currently believed. In addition, combinations of vaccines have potential risks that have never been explored. I clearly understand the public health import of diseases we are preventing, but we need prospective studies.

Finally, licensing boards need to be less heavy-handed to doctors offering off-label treatment to families that are desperate for treatment. Off-label use of medications is common in all fields of medicine. The standard by which these physicians should be judged is risk versus benefit.

Thank you for your time.

[The prepared statement of Dr. Segal follows:]

Testimony Parent / Physician: Autism
Jeffrey Segal, MD

In October 1999, I became a member of a club I never wanted to join. My son was given a diagnosis of regressive autism.

Introduction

A little background. I am the father of 4 year old twins, a boy, Joshua, and a girl, Jordan. I practiced as a neurosurgeon in Indiana. My son, developed normally and hit all of his milestones. He was jolly, sweet-natured, and very bright. Before his second birthday, he started losing the language he had acquired. He became hyperactive and inattentive. Finally, he lost interest in his toys, videos, and his sister withdrew socially. We thought he might be deaf. By the time a physician confirmed the diagnosis, my wife, Shelley, and I already knew. We were shocked and devastated. Fortunately we knew a couple who had recovered their child from autism and followed their lead as it related to treatment. This is what parents do after being handed the diagnosis. They network with each other for information because there are few standardized treatment plans. I investigated treatment options. The first treatment consisted of occupational therapy to address my son's sensory issues. The other early intervention that we opted for was called ABA (Applied Behavioral Analysis). ABA breaks down everyday actions into discrete steps. The training is delivered as one on one therapy and involves 40 hours of work a week. It is expensive, exhaustive, and time consuming. Most families we spoke with in Indiana were on waiting lists for ABA treatment. Time was our enemy. We moved to North Carolina. I quit my practice and devoted my time to analyzing and investigating biomedical options.

I am pursuing three main projects right now:
First, help my son. If I can help him, I can help others.
Next, research toxicologic causes and treatments as it relates to autism. Some of this work is in cooperation with Dept of Physiology at Wake Forest School of Medicine.
Finally, I am exploring pharmaceutical solutions. I started a drug company based on medications that are likely to be relevant to helping those with autism. (Should also help those with Parkinson's, schizophrenia, and other central nervous system disorders.)
I do not have time to practice neurosurgery any longer......

Observations

(1) More children today are developing illnesses earlier in life. Autism and a host of autoimmune disorders are becoming rampant. Anecdotally, I live within 3 walking minutes of a child with juvenile diabetes, another child with an autoimmune platelet disorder, and another child with pervasive developmental disorder. Each child became ill in their second year of life.

The number of children with autism or related disorders is rising. We are in the midst of a dangerous epidemic. Don't take my word for it and don't ask physicians. Ask teachers. These kids are filling regular and special ed classrooms to overcapacity.

Some argue that the number is static and doctors are just better diagnosticians. Two points: Where are the autistic adults who were never diagnosed 20 years ago? Surely they must be somewhere. Also, physicians spend less time than ever truly talking with patients and families. More diagnoses are made by tests and machines. No laboratory test exists for autism. The diagnosis is based strictly on clinical examination. And finally, the average time between onset of autistic symptoms and diagnosis is still years. We are not better diagnosticians.

The California Dept of Developmental Services is now adding one new child with full blown autism every 3 hours. It costs $2 million to raise an autistic child to age 21.

(2) The number of physicians who have a deep understanding of autism treatment is small. These doctors are overworked and it takes months to get an appointment. Many of these MD's have affected children of their own. Often they don't work at high profile medical centers. Since autism is a systemic condition that involves the gastrointestinal system, immunologic system, and central nervous system, it requires expertise by multiple specialists. Finding these specialists who have an interest in treating autism can be a daunting task.

(3) The statistics quoted by academicians are at odds with current reports by parents. For example, the standard autism literature does not recognize a general connection with gastrointestinal disease and autism. However, families report that 80% of their children have GI problems. Standard literature suggests that only 20% of autistics have the regressive variety; that is, they developed normally until age two, then regressed. Most parents report that their children fall into the regressive, or acquired, category.

(4) Andrew Wakefield has theorized about a connection between GI problems and autism. His work suggests that the measles virus (from vaccines) might persist in GI tissue. This association might also have a causal role in autism. This work urgently needs replication. Yet, many gastroenterologists conveniently dismiss his work rather than test his theory.

(5) 80% of autistic children have abnormal spike activity in brain regions associated with speech. It is believed that those electrical abnormalities might contribute to the language deficits. Correct diagnosis requires, at a minimum, an overnight EEG. Most kids are given a one hour EEG, informed that it is normal, and never properly treated. Not infrequently, the EEG is normal, though a more sensitive test, the MEG, is abnormal. MEG is located in only a handful of cities and is expensive. Insurance companies do not readily pay for this test. Once correctly diagnosed, many children may be given appropriate antiseizure medication. This often improves the language deficits.

(6) Insurance companies do not readily pay for anything that is autism-related. Laboratory tests are paid out-of-pocket by parents. And most autism research is being performed at the parent's expense. They pay for the tests and the consequent data is collated for study. This is opposite of the way research is traditionally done.

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(7) ABA treatment is effective for about 50% of the autistic children. It calls for early intervention and intensive one-on-one therapy. It is expensive, but worth it. Costs are $30-70,000 a year. Parents turn to school districts to make these treatments available. Where one resides determines the type of treatment received. It is not uncommon for the school district to litigate against parents so they won't have to provide that service. The alternative is placing children in large classrooms. This effectively warehouses the child and minimizes potential for future gain. Waiting lists for services are all too common.

(8) Most physicians are reluctant to do more than provide band-aids for symptoms; such as providing antipsychotic medications to control difficult behaviors. Parents are told no data from double blind controlled studies supports existing therapies. We don't have time to wait for these studies. The clock is ticking. Most recommended standard treatments are not particularly high risk. Research must be done to advance the field. But, there is a paucity of treatments that are being studied and examined.

(9) There is a serious need to study probable role of environmental agents as causative factor in autism. Toxins, vaccines, and infectious agents must be considered.

The Centers for Disease Control recently reported that one in 10 women of childbearing age in the U.S. are at risk of having newborns with neurological problems due to mercury exposure. Until recently, vaccines had thimerosal as preservative. Thimerosal is a preservative that contains organic mercury. Organic mercury is widely recognized as a neurotoxin. It damages tubulin, a major structural component of cells (Liliom, 2000). Infant vaccines that routinely contained thimerosal were DPT, Hep.B and HiB. Following the CDC recommended vaccine schedule infants were exposed anywhere from 0 to 187.5 mcg of ethyl mercury, depending on the vaccine manufacturer and total exposure through 18 months could be as high as 237.5 mcg. The dose thought to be allowable by EPA is 0.1 mcg per kilogram per day. If an average 5 kg infant received all thimerosal containing vaccines at his 2 month visit the exposure that day would be 62.5 mcg ethyl mercury, an exposure that is 125 times over the EPA's guideline.

Information from large epidemiological studies conducted in mercury exposed populations suggests that intermittent large exposures may pose more risk than small daily exposures. In one study, lower scores on memory, attention, language and motor function tests were found years later in children who had been exposed prenatally to intermittent bolus doses of methyl mercury. The doses were from dietary exposure at levels that had been previously thought to be safe. (Grandjean, 1998)

At the June 21, 2000 Advisory Committee for Immunization Practices meeting held in Atlanta, Georgia, Dr. Thomas Verstraeten of the National Immunization Program presented a review of vaccine safety datalink information on thimerosal containing vaccines. Over 400,000 children participate in the vaccine safety datalink program. From this database 100,000 eligible charts were reviewed to determine exposure to thimerosal containing vaccines and specific neurodevelopmental outcomes. Key findings were statistically significant associations between cumulative exposure to thimerosal containing vaccines at 2 months of age and unspecified developmental delay; 3 months of age and tics; 6 months of age and attention deficit disorder; 1,3,and 6 moths of age and speech and language delay and neurodevelopmental delays in general.

The vaccine manufacturers have stopped making new vaccines with mercury as a preservative. But, many vials still sit on MD's shelves. To date, the FDA has denied requests from concerned citizens for a recall. With more vaccines being recommended to an already full vaccine schedule, and many vaccines administered earlier in life, the potential for mercury toxicity in children is high. The symptoms of mercury poisoning and autism are quite similar. In addition, mercury is prevalent in the environment and finds its way into the food chain.

Other metal toxins may play a role in autism. I recently analyzed 250 hair samples and found 30% have over 2 SD above mean for various metals: aluminum, arsenic, or antimony. These agents are ubiquitous in the environment. This finding is timely. The Bush administration had reservations about lowering acceptable safe limits of arsenic in the water supply.

Chelation treatment is one way to remove metal toxins from the body. Chelation uses compounds that have a propensity to grab metal toxins. There are many unanswered questions regarding chelation as it relates to treating mercury intoxication. Does it cross the blood-brain barrier? Is it effective for chronic poisoning? It is considered an alternative therapy, yet it appears to help a large number of children. Historically, chelation's reputation is poor. I say this as a physician who would never have previously entertained the idea of chelation for any chronic condition. It is extraordinarily difficult for a practitioner to get funding to study chelation. It is just as difficult to get MD's to consider it as a viable treatment..

My scientific work is focused on analyzing genes and proteins that detoxify heavy metals in autistic children. My hypothesis is that some children are genetically predisposed to the inability to detoxify the metals to which they are exposed to in the environment. These metals may come from vaccines, food, or the environment. The major detox pathway for heavy metals is (metallothionein) MT. I am researching whether or not children have defective MT genes or if they are unable to make appropriate amounts of this protein in response to insult. This could explain why not all children exposed to the same environmental insult develop autism.

Recommendations
I'd like to close with several concrete recommendations:

- Immediate and abundant funding for research, particularly treatment.
- Fund fellowships to increase the number of skilled MD's treating autism.
- Mainstream autism as it relates to insurance payments. It is a biological condition (not a psychiatric one) and should not be constrained by policy limits on mental health coverage.

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- Standardize payments for ABA across the country. It is unfair that some families are on waiting lists for two years to access coverage.
- Get vials of thimerosal-containing vaccines off the shelves through recall.
- We need to seriously test the hypothesis that vaccines are not always as safe as is currently believed. In addition, combinations of vaccines have potential risks that have never been explored. I understand the public health import of diseases we are preventing, but retrospective statistics trying to prove an underlying bias is intellectually dishonest. Prospective studies are needed.
- Licensing boards should be less heavy handed to MD's offering off-label treatment to families that are desperate for treatment. Off-label use of medications is common in all fields of medicine. The standard by which they should be judged is risk versus benefit.

Summary:

Today we are losing a generation of children to autism and related disorders. As a physician and scientist, I work diligently to provide the answers that will unlock autism's mysteries. As a parent, I am a detective. I work with my wife and my exceptional team of ABA, occupational, and speech therapists to discover what will ultimately heal my son. I have great faith in Josh's courage and determination.

I recommend that all parents put their children on a gluten free / casein free diet to improve focus and cognition. It has minimal risk and many children have responded. Parents should perform 24 hour EEG on their child to detect possible seizure or spiking activity in the brain. And parents should test their children for heavy metal toxicity. DMSA has been shown to help a number of children. The reason for this improvement may be entirely unrelated to its action as a chelating agent. Nonetheless, I would encourage parents to consider a trial of this treatment under the auspices of their doctor.

Every day Shelley and I struggle in our continual battle to fight Josh's sensory, social, and cognitive impairments. Jordan, his twin sister, helps him also. It is our greatest hope that one day our children will not only share a classroom, but the close, playful, and loving relationship they experienced before Josh was robbed by autism.

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Mr. BURTON. Before we go to the next witness, let me tell you that every Congressman who got a flu shot from the Capitol Hill physician—they do not know this—but they all had thimerosal injected into their bodies. They all had mercury put into their bodies. I got the shot and afterwards I looked at the insert and found that.

There are a lot of people who believe—like you do—that a number of senior diseases, like Alzheimer's, could be contributed to by us having injections of mercury. And nasal sprays the doctor gave me, the preservative was thimerosal. So we are getting mercury in all kinds of things, not just for children, but for adults as well.

So to my colleagues, if you had a vaccination for flu—and I went over to see the doctor, who is a wonderful doctor and a good friend, and he did not know it was in there.

Dr. SEGAL. And it is followed with a tuna fish sandwich, to boot. [Laughter.]

Mr. BURTON. Now, do not start telling me I cannot eat tuna fish. [Laughter.]

Dr. Humiston.

Dr. HUMISTON. Thank you for inviting me to speak on behalf of my son, Quinn.

I wish you could meet Quinn. He has big eyes as brown as chocolate, and when he grins, you see those two big front teeth. He has the smooth, lean, muscular limbs of a child for whom movement is perpetual. You would never guess when he is sleeping that with that perfectly handsome face and that perfect 8-year-old body that Quinn has almost no language, that Quinn will bite and claw people in fits of aggression, which at times, appear as spontaneous and uncontrollable as a seizure, and that Quinn, on a bad night, can get along on as little as 3 hours of sleep.

You think you have all the answers until you become a parent. I did not even know all the questions. The main question my husband and I have had to address is, what are we going to do now to help?

We initially decided to use behavior analytic treatment, an educational technique derived from research on operant condition. A one-on-one therapist gives the child short and clear instructions for a desired behavior. For example, Say "Hi." A correct response gets an immediate reward. For example, the therapist smiles and says, "Great job." An incorrect response may be ignored or may trigger the therapist to prompt the child. As recommended, Quinn received 40 hours each week of one-on-one therapy. Studies at UCLA had shown that many children had significant improvement with this technique and replications at three other sites confirmed their findings.

When I say this, it sounds so rational. We were faced with this devastating diagnosis and we went through the literature and talked to every expert we could find. We found an intervention on which there was encouraging evidence, so we threw ourselves, day and night, into getting and keeping the therapy in place. I assure you that it did not feel rational at the time. I had the panic-stricken urgency of a person staring down the barrel of a gun. My son's brain development, I believed, depended on me finding the right therapy in time before we was too old to be helped.

Autism and mercury experts at the University of Rochester have advised us not to get chelation therapy for Quinn. I was told that chelation is not recommended even for acute mercury poisoning. Brain damage done by mercury poisoning is irreversible. You do not see improvement after chelation. Finally, I was told that the safety of this intervention is not known.

My husband and I have tried other interventions: a phenol-free diet, a gluten-free and casein-free diet, medications including Ritalin and Prozac, and cranio-sacral massage. We tried to get secretin and found a place where we could get a dose or two for $10,000, but by then evidence was accumulating that it was not effective.

There have been more questions. Because I am a pediatrician, and particularly because I used to work for the CDC National Immunization Program, many people have asked me if MMR causes autism. As you are well aware, two exhaustive independent reviews have become available on that topic. The American Academy of Pediatrics, of which I am a fellow, has made a summary of their review available to all pediatricians. They report that the available evidence does not support the hypothesis that MMR vaccine causes autism or associated disorders. Separate administration of measles, mumps, and rubella vaccines to children provide no benefit over administration of the combination MMR vaccine and would result in delayed or missed immunizations.

The American Academy of Pediatrics is dedicated to the health, safety, and well-being of children. The AAP has proven itself to be absolutely dedicated to vaccine safety. They quickly withdrew their recommendation for rotavirus vaccine at the first sign of a problem and recommended the move away from thimerosal-containing vaccines even during the information-gathering period.

These actions have given me added assurance of their open-mindedness regarding the MMR-autism hypothesis and have added weight to their findings.

Similarly, the Institute of Medicine, the supreme court of medicine, convened the Immunization Safety Review Committee to address this issue, and they found “that the evidence favors rejection of a causal relationship at the population level between MMR vaccine and ASD.” The committee felt that the relationship been MMR and autism would be extremely rare, if it occurred at all.

The next question is about thimerosal. And we all look forward to IOM’s review of this topic. I am aware of an interesting recently published report from the University of Rochester that shows that none of the blood mercury levels observed in full-term infants studied shortly after vaccination exceeded the most recently revised lowest level of maternal blood mercury considered to represent potentially significant exposure to the developing fetus.

So what are we going to do now to help? Despite intensive therapy, my son has not been helped dramatically. And that is why I am here today. I am absolutely certain that we need more research. I am pleased that IOM was asked to review the question of MMR and autism, and I am pleased that they will review the thimerosal question. I am pleased that NIH is proceeding with the scientific evaluation of alternative and complementary medicine. I am delighted with the progress made by the collaborative programs of excellence in autism and I trust that funding is assured for the future.

I am excited by the creation of the congressional Coalition for Autism Research and Education and most especially by the Children's Health Act of 2000. I am encouraged to hear that the CDC has created a new Center on Birth Defects and Developmental Disabilities. All this activity is especially heart-warming for a parent because autism research has been significantly neglected up to now.

We need good autism epidemiology in the United States to determine risk factors and true rates. We need basic science research into the nature and causes of this disorder. And we need clinical research to determine what works and what does not, what is safe and what is not.

As we all know, appropriations are the key. A financial investment now could, in maybe just a few years, prevent another mother from having to face the questions I have had to face. There is a motto: "You can have it fast, good, or cheap, pick two." In autism, research, we cannot afford to go slowly or have poor quality. That is why parents want Congress to fund high-quality research at the high level it deserves given the disorder's frequency, its devastation, and notable past neglect.

And we need significant research funding that comes with a commitment to the long term. Scientists are poised on the brink of success, but it may not come tomorrow. Like the families of autistic people, Congress has to be in this for the long haul.

How should the autism research agenda be set? Foremost, scientists should be encouraged to follow the cues of epidemiology and basic research. Listen to parents carefully, but do not neglect to follow through based on the leads from science.

Autistic families need better services—educational services for the autistic individuals, parent training for handling autistic offspring through their lifetime, and respite services that are so essential in coping. Finally, parents need to see residential care facilities in place that will help with the question my other child asked me, what is going to happen to Quinn when you and Daddy die?

The question for this committee and all of us is the same as the initial question my family faced, what are we going to do now to help?

[The prepared statement of Dr. Humiston follows:]

Testimony of Dr. Sharon Humiston

Introduction

I wish you could meet my Quinn. He has big eyes, as brown as chocolate, and when he grins you see those two big front teeth. He has the smooth, lean, muscular limbs of a child for whom movement is perpetual. You would never guess when he's sleeping – with that perfectly handsome face and that perfect 8-year-old body --

- that Quinn has almost no language,
- that Quinn will bite and claw people in fits of aggression, which, at times, appear as spontaneous and uncontrollable as a seizure,
- that Quinn, on a bad night, can get along on as little as three hours of sleep.

Answering questions

You think you have all the answers to good parenting until you become a parent. I didn't even know all the questions. The main question my husband and I have had to address is: What do we do now?

We decided to use "behavior analytic treatment" – an educational technique derived from research on operant conditioning. A one-on-one therapist gives the child short and clear instructions for a desired behavior (for example, "Say 'Hi.'"). A correct response brings an immediate reward (for example, the therapist may smile and say "Good job!"). An incorrect response may be ignored or may trigger the therapist to prompt the child. As recommended, Quinn received 40 hours each week of one-to-one treatment. Studies at UCLA had shown that many children had significant improvement with this technique and replications at three other sites confirmed their findings.

When I say this, it sounds so rational. We were faced with this devastating diagnosis and we went through the literature that was available and we found an intervention on which there was encouraging evidence so we threw ourselves – day and night – into getting and keeping the therapy in place. I assure you it did not *feel* rational at the time. I had the panic-stricken urgency of a person staring down the barrel of a loaded gun. My son's brain development, I believed, depended on me – on me finding the right therapy in time, before he was too old to be helped.

There have been more questions. Because I am a pediatrician, and particularly because I used to work for the CDC National Immunization Program, many people have asked me if MMR causes autism. Recently, two exhaustive reviews have become available on the topic.

The American Academy of Pediatrics has made a summary of their review available to members. They report: "The available evidence does not support the hypothesis that MMR vaccine causes autism or associated disorders…Separate administration of measles, mumps, and rubella vaccines to children provide no benefit over administration of the combination MMR vaccine and would result in delayed or missed immunizations." The AAP has proven itself to be absolutely dedicated to vaccine safety; they quickly withdrew their recommendation for rotavirus vaccine at the first sign of a problem and recommended the move away from thimerosal-containing vaccines even during the information-gathering period. These actions have given me

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added assurance of their open-mindedness regarding the MMR/autism hypothesis and have added weight to their findings.

Similarly, the Institute of Medicine (the Supreme Court of Medicine) convened the Immunization Safety Review Committee to address this issue and they found "that the evidence favors rejection of a causal relationship at the population level between MMR vaccine and ASD."

With this behind us, the next questions arise about vaccines and mercury and chelation therapy for autism. I am not an expert on these topics, but as a parent of an autistic child you learn to be bold about hunting down experts who are willing to talk to you. Where I work now, at the University of Rochester, I was able to find such experts. They explained to me that the federal guidelines have a large margin for safety built in to them, so even if a child retained the whole dose of mercury from vaccines, the retained load of inorganic mercury would be lower – by a factor of 10 -- than has ever been shown to cause symptoms. A recent study from University of Rochester shows that none of the blood mercury levels observed in the full-term infants studied exceeded the most recently revised lowest level of maternal blood mercury considered to represent potentially significant exposure to the developing fetus.

I was not advised to get chelation therapy for Quinn. I was told that chelation is not recommended even for acute mercury poisoning. Brain damage done by mercury poisoning is irreversible – you do not see improvement after chelation. Finally, I was told that the safety of this intervention is not known.

Although we have not tried chelation, my husband and I have tried other interventions: a phenol-free diet, a gluten and casein-free diet, medications (Ritalin and then Prozac), and cranio-sacral massage. We tried to get secretin – and found a place where we could get a dose or two for $10,000, but by then evidence was accumulating that it was not effective. Why have we tried all this? That leads to the question most frequently asked: How is your son doing?

What we need: Help answering the questions

My son has not been helped dramatically. And THAT is why I am here today. I am absolutely certain that we need more research.

I am pleased that IOM was asked to review the question of MMR and autism and I am pleased that they will review the thimerosal question. I am pleased that NIH is proceeding with the scientific evaluation of alternative and complementary medicine. I am delighted with the progress made by the NICHP Collaborative Programs of Excellence in Autism and I trust that their funding is assured for the future. I am excited by the creation of the Congressional Coalition for Autism Research and Education and, most especially by the Children's Health Act of 2000. I am encouraged to hear the CDC has created a new Center on Birth Defects and Developmental Disabilities.

All this activity is especially heart warming for a parent because autism research has been significantly neglected up to now.

- We need good autism epidemiology in the U.S. AND
- We need basic science research into the nature and causes of this disorder AND
- We need clinical research.

As we all know, appropriations are the key. A financial investment ***now*** could – in maybe just a few years – prevent another mother from having to face the questions I have had to face.

There is a motto: "You can have it fast, good, or cheap – pick two." In autism research, we cannot afford 'slow' or 'poor quality.' That's why parents want Congress to fund this research to the high level it deserves given the disorder's frequency, its devastation, and its notable past neglect.

And we need significant research funding that comes with a commitment to the *long term*. Scientists are poised on the brink of success, but it may not come tomorrow. Like the families of autistic people, Congress has to be in this for the long haul.

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Autistic families need better services – educational services for the autistic individuals, parent training for handling autistic offspring through their lifespan, and respite services that are so essential in coping. Finally, parents need to see residential care facilities in place that will help with the question my other child asked me,

"What is going to happen to Quinn after you and Daddy die?"

Mr. BURTON. Let me just say that I admire your view, Doctor, that the health agencies are doing a good job. And I think for the most part they are, but I would like to bring to your attention that the rotavirus vaccine—the advisory committee that recommended that—was kind of split. Some of the people thought there should be more testing done on the rotavirus vaccine. But the chairman of the committee had financial interests in the company that manufactured a rotavirus vaccine.

Dr. HUMISTON. The chairman was John Motley, who had no conflicts of interest at all.

Mr. BURTON. Let me just tell you that we have already checked. We looked at the financial disclosure forms. The chairman——

Dr. HUMISTON. It could not have been the Chair. He has no——

Mr. BURTON. Well, there were a number of people on there who had financial interests in the rotavirus vaccine. And that vaccine was put on the market. Within a year, we had one child die and a number of them had serious problems. We are looking at and have found some financial conflicts of interest among other people who are in the decisionmaking process.

That is one of the reasons why many people in Congress are very concerned about things like the report we just received. And that report was not categorically saying that the MMR vaccine was not a cause of autism. It did not conclude that, if you read the whole report.

Let me just ask a couple of questions here.

First of all, does the MMR vaccine, when it is being produced, does it include in any way in the production mercury? Do any of you know that?

Dr. HUMISTON. It does not. MMR does not contain thimerosal. It contains no preservative because it is a live vaccine.

Mr. BURTON. I am asking in the manufacture of it because in the manufacture, we have been told—and I do not know that it is true—there was mercury in some of the production of the vaccine.

But you are saying that categorically, that is not——

Dr. HUMISTON. No, because it is a live vaccine. The live vaccines do not need preservatives.

Dr. SEGAL. I would say that we do not know. I would say also that in the manufacture of the drug we are working on, there is mercury in the process and we take pains to remove it at the end. We think that it is all out.

But I think the answer to your question is that we do not know. I do not know that——

Mr. BURTON. But there is mercury used in the process?

Dr. SEGAL. I do not know. I do not think anyone here knows.

Mr. BURTON. We want to check on that and find out about that.

Mr. Bradstreet, are you stating that the combination of the thimerosal-containing vaccine with the MMR vaccine causes neurologic, immune, and GI problems in susceptible children?

Dr. BRADSTREET. I think that would be incomplete, but I am saying that in part.

I think there are a number of environmental factors that are skewing the child's immune system toward a predilection along the autoimmune lines. I think that thimerosal is one of those issues. The aluminum adjuvants is another issue.

Then the other vaccines I discussed—the Hepatitis B vaccine and HiB—also are capable, as is pertussis—of pushing that TH–2 response so that by the time we get to the 15-month level or so and we give the MMR vaccine, it is the next TH–2 potential responding vaccine that the kids get. For some of the kids, it is just too much.

However, I have a number of kids who, immediately after the Hepatitis B vaccine—within days—seem abnormal and never recover and evolve autistic-like symptoms. I have heard the same thing after pertussis.

So it is not just MMR by any means, but there is a significant number—perhaps half of our families—who now claim they had a perfectly healthy child and within days—10, 14 days, whatever—their child was completely changed following the vaccine schedule.

That, in and of itself, is not conclusive. But it certainly causes one to look very, very hard at that subject. Epidemiology, in and of itself, is not going to give us that answer.

Mr. BURTON. You talked about the mercury. That was in the Hepatitis B vaccine as well?

Dr. BRADSTREET. Yes, as well as in the HiB vaccines. Almost all the HiB vaccines have mercury in them as well. So those are multiple sources for mercury.

Mr. BURTON. That is exactly what happened with my grandson, within days after his.

Dr. Bradstreet, are you seeing improvements with the treating of children to remove mercury? Do these children appear to be more vulnerable to other toxic metals?

Dr. BRADSTREET. I think that something—and I am not sure what it is at this point in time—has wounded the body's normal and natural metallic defense. We have a system in the body designed to prevent environmental toxins like mercury and lead and other things from being toxins within the body. Many things protect the body. However, for whatever reason, certain children seem to be unusually vulnerable to that.

There is abundant data now available that individual variability at the time of the mercury exposure to thimerosal—we do not know how susceptible that child is. We do not know what other sources of mercury he has had, whether it was RhoGAM or diet or environment. We do not know how much he is going to get. And we do not know the status of his ability to defend against that mercury. We kind of cavalierly give it assuming that because it is below some sort of EPA threshold—although, with the combination of the multiple vaccines that is not true—that it is going to be safe.

I think that there is something about certain children that makes them very vulnerable to mercury.

Mr. BURTON. I have some more questions.

Mr. Horn.

Mr. HORN. Thank you, Mr. Chairman.

Dr. Segal, I believe you mentioned RhoGAM, and the content of thimerosal.

Dr. SEGAL. That is accurate, yes.

Mr. HORN. What would be the behavioral changes if one used that consistently?

Dr. SEGAL. I am not sure I understand that question, but let me take a stab at it.

The medication is RhoGAM, which would be given to RH negative mothers to prevent a reaction with children in terms of attacking their blood cells.

Thimerosal is used as a preservative. It is given to the women—at this point—while they are still pregnant. The mercury preservative would be able to cross through the placenta and get into the developing infant. The theory would be that it would harm the developing fetus, at which point you would see neurodevelopmental abnormalities.

Mercury is an accumulative problem. That is, as you continue to be exposed to mercury, the body struggles with trying to remove it. When it builds up to some critical level, which cannot be predicted in the individual child, we have the potential to see neurodevelopmental problems.

Mr. HORN. So this is nothing to do with Rogaine, which relates to hair, and so forth? [Laughter.]

Dr. SEGAL. Not to my knowledge.

Mr. HORN. You have 2 million people across America who will wonder.

Dr. SEGAL. I think they can rest comfortably. [Laughter.]

Mr. HORN. Dr. Segal, do you think the genetic component of this problem may be the inability to these children to clear toxins and metals from their bodies?

Dr. SEGAL. I think that is the first step. I think there are multiple problems that are individually necessary but not sufficient. I think the first step is a genetic predisposition. I think that predisposition relates to the ability to detoxify against environmental insults.

Mr. HORN. Do you agree with the comparison of the symptoms of autism and the symptoms of mercury toxicity as similar? Do you see that?

Dr. SEGAL. I think the parallels are astounding, yes.

Mr. HORN. And that has been a lot of your research?

Dr. SEGAL. That is correct.

Mr. HORN. So you are speaking from scientific research?

Dr. SEGAL. That is accurate, yes.

Mr. HORN. Thank you very much for your testimony. I was very interested in it.

Dr. Schneider, are you seeing children with increased toxicity to other substances, such as arsenic?

Dr. SCHNEIDER. Absolutely. My own children have high levels of arsenic. After some research, I learned that is because I live in the State of Arizona where mining has been and still is occurring and our water supply comes from Colorado where the same can be said. Gold is mined with cyanide. Copper is minded with arsenic. It is so prevalent in the Phoenix water that no one is using Phoenix water. We have to get our water from Colorado, which really is not much better.

I have a reverse osmosis system in my household, and I mistakenly thought that removed heavy metals. I found recently that was not correct. I had to pay $5,000 to put in a water system which did remove arsenic and mercury from our water supply.

Mr. HORN. That is the Phoenix water system?

Dr. SCHNEIDER. Yes.

Mr. HORN. Do you see that throughout Arizona?

Dr. SCHNEIDER. I have not looked throughout Arizona, but certainly there are metal-toxic children throughout Arizona.

Mr. HORN. We see the same thing in Los Angeles where we have had various types of industries, small and large, where the metals just get into the underground water supply. That has become a major problem. I know EPA has studied this. What studies have you seen that lead to a different—arsenic as it goes around—some say you cannot deal with it because it is in this or that. I just wonder what kind of research you have seen where it is clear that it is hurting people substantially.

Dr. SCHNEIDER. Quite honestly, I do not do that kind of research and I am not as familiar with it as I intend to be because I was focusing more on the mercury aspect. But I find now that mercury is not our only problem. We are exposing our population to many toxic metals.

Mr. HORN. We understand that typically children with autism are first diagnosed by a developmental specialist or psychiatrist and that the physical problems with these children are not addressed.

What do you think must be done to ensure that these children receive appropriate medical care?

Dr. SCHNEIDER. At our research center, we have initiated a physician outreach program, which is now in the stages of developing educational material for physicians, planning conferences for physician education. The reality is that most parents diagnose their children and then go to their pediatrician who tells them that they do not think so. Then they go back again and eventually get referred to the proper specialist and have the diagnosis confirmed.

In my own case, our pediatrician is a dear friend of mine and I have the greatest respect for him, but he did not know autism when he saw it. And that is very, very typical. We need to change that because, as many of us know, the earlier the child is diagnosed and the earlier the intervention is begun, the better the child's chances of having a partial recovery.

My own children are 8½ and 9½ years old now. I would say the clock is ticking.

Mr. HORN. In some of Chairman Burton's earlier hearings, we found there were a lot of medical journals of which there are probably a couple hundred—I have seen them in our library in Long Beach—that have glowing reports of this or that and they do not really tell you the effects on it. Do you have some feelings that the various professional groups and segments of this and that specialist, and some of their yearly meetings—they ought to have meetings that relate autism to all of the things that they might not—they go through medical school and there is great ignorance there in many ways, just like nutrition was, which was a simple thing. Doctors ought to know something about nutrition. Well, doctors ought to know something about this.

Now, how do we communicate with them where they read it, and they see it, and it means something?

Dr. SCHNEIDER. You are absolutely right because the reality is that pediatricians or family practitioners were not educated in the area of autism. Their image of autism is a child rocking and banging his head on the wall. Many of our children do not do that, thank goodness, yet still have autism.

So the physician outreach is a very important project for us. But what we realized when we spoke to the residency programs in our city is that pediatricians in training right now—a pediatrician has 4 years of college, 4 years of medical school, and 3 years of residency—in that training process, they talk about developmental disabilities for about 1 month, and autism is only one portion of their focus. So there really is very little exposure to this area.

If you think about what happens in terms of medical education after training, it is primarily in the form of conferences. I am sorry to say that most conferences are sponsored wholly or in part by pharmaceutical companies. The message they want to get across has much to do with treatment of the condition for which they have a drug.

So you have to understand that it is up to the physician to educate himself or herself after training and to take into account the sources of the information they are receiving.

Mr. BURTON. Thank you, Mr. Horn.

Mr. HORN. Thank you.

Mr. BURTON. I will tell you my son-in-law is a doctor. And many doctors pretty much take at face value the recommendations and the research done by the CDC and the FDA. I can tell you that even here on Capitol Hill—like I was talking about the vaccine we get for the flu—I do not think any doctors up here even knew that there was mercury or thimerosal in it.

Mr. Blagojevich.

Mr. BLAGOJEVICH. Thank you, Mr. Chairman.

Dr. Humiston, our staff has just checked with Merck, the only licensed manufacturer of the MMR vaccine. The staff was told—and perhaps you can confirm this—that there is no mercury in that vaccine. Is that consistent with your understanding?

Dr. HUMISTON. Yes. My understanding is that there is no mercury and there is no mercury in the process of making it. It is thimerosal-free, as opposed to the vaccines that have mercury in the process but not actually in the vaccine.

Mr. BLAGOJEVICH. Thank you very much.

Thank you, Mr. Chairman.

Mr. BURTON. We will check on that.

Dr. Weldon.

Mr. WELDON. Thank you, Mr. Chairman.

I have a question for Dr. Bradstreet.

You have been doing a lot of research—and really any of you can comment on this—and you have talked to a lot of researchers. Have you encountered any lack of willingness or intimidation to research in areas that might suggest that there are problems with vaccines in terms of its impact on the careers of researchers or their ability to get funding in the future? Have you encountered any comments to that effect?

Dr. BRADSTREET. Yes. Actually, we work with researchers at several major university medical schools around the country. Many of them or their department chairmen have related back to us that there is significant fear and apprehension about doing a study that looks into vaccine safety for fear of being blacklisted by the pharmaceutical industry for future funding of research. Many pediatric departments or infectious disease or immunology departments around the country at medical schools are completely dependent for a vast majority of their research budget and operating expenses on granting from the vaccine manufacturing companies. Many of those vaccine manufacturers make a host of different drugs.

If you look then at the potential liability issue—determining for example that thimerosal may be harmful to children—what that means from a liability perspective, a beginning of life neurologically damaged child that has a life expectancy similar to yours or mine, 70 or 80 years of care—that is cataclysmic. So they will go a long way to potentially suppress research along these lines.

It is something that needs to be addressed and there need to be independent sources of funding completely apart from the drug companies.

Mr. WELDON. Have any of the other witnesses encountered comments to that effect? Or would you rather not comment on this issue?

Dr. SEGAL. I would rather not comment on that issue. I would say, without getting into detail, the answer is yes. We have encountered that difficulty. But as we are trying to make in-roads in terms of additional research projects, I feel any comment I could make would be fragile.

Dr. HUMISTON. At the University of Rochester, because my developmental pediatrician is one of the researchers for the centers of excellence, I am aware of what they do. They are getting funding to look at vaccine safety issues.

Mr. WELDON. I have a question about the incidence.

The incidence in boys is four times higher than the incidence in girls. The incidence in the population is estimated at being—some say as high as 1 in 100—most likely 1 in 500 or somewhere in between, according to a lot of researchers. But that doesn't that mean that the incidence in boys is substantially higher? Aren't we talking about it being somewhere between 1 in 50 and 1 in 250?

Dr. BRADSTREET. Just to be specific, we are talking about prevalence, which is the amount of disease in the population of children or boys. Incidence would be the new cases that are coming on-line per population on an annual basis. That is probably very high as well, although there is much less incidence research being done as compared to prevalence.

We know that it is very prevalent. A lot of children have this. If you look at Oregon as an example—and all the citations are on pages 5 through 8 of my testimony—clearly Oregon is very conservative. The State is run by a physician.

Mr. WELDON. If I could interrupt you for a second, the Oregon data you showed was less than 1 in 200. Is that correct?

Dr. BRADSTREET. Yes, 1 in 190 in Oregon.

Mr. WELDON. What does that make it in boys?

Dr. BRADSTREET. It is probably something like 1 in 50 or 1 in 70 in boys if you factor the four to one difference in occurrence rate in boys.

Mr. WELDON. Dr. Segal, you kind of made the comment as a joke, but this issue—I have had CDC officials in my office talking about whether we have an epidemic or not, and they cite how the DMS–

3 was changed. But you made an excellent insight. If we are just diagnosing it better, what happened to all the adults? Is anybody researching that or looking into that?

Dr. SEGAL. If it is a question of diagnosis, the adults have to be somewhere. They did not disappear. The problem is that they are not there. The numbers have gone up. I think that is the only conclusion we can make.

Mr. WELDON. But nobody has done a research study looking at adults who are in institutional care, have some kind of psychiatric disability, who were perhaps previously diagnosed as mentally retarded, who may have actually had autistic spectrum disorders. Nobody is looking into that, to your knowledge?

Dr. SEGAL. To my knowledge, no one is. I would comment that Dr. McDougle, when he was at Yale, had a great deal of interest in adult autistic patients. So he may be able to comment on that further. He will be in the third panel.

Mr. WELDON. I know I am running out of time. I just have a question for Dr. Humiston.

You quoted from the IOM study that the committee concludes that the evidence favors rejection of a causal relationship at the population level between the MMR vaccine and autistic spectrum disorder. I fully expected them to say that because if they did not say that and it got out in the press, then parents all across America would start rejecting the vaccine and we could have a huge explosion of measles.

But then they did go on to say in the next section that they did note that their conclusions did not exclude the possibility that MMR vaccine could contribute to ASD in a small number of children because the epidemiologic evidence lacks the precision to assess rare occurrences.

I assume you agree with that section of the report as well.

Then they further went on to recommend further areas of research—and they have several areas of research they recommend—to include to develop targeted investigation of whether or not measles vaccine strain virus is present in the intestines of some children with ASD.

Essentially, they are calling for what I had encouraged them to do when I testified before them, to encourage NIH to fund the duplication of Dr. Wakefield's and O'Leary's work.

I assume you have seen Dr. Wakefield's micrographs and slides of inflammatory bowel disease in these kids, and you have reviewed Dr. O'Leary's PCR research showing the presence of measles virus particles in the intestines of these kids.

Dr. HUMISTON. I have not reviewed his micrographs. I am not a gastroenterologist. I am an emergency medicine pediatrician.

Mr. WELDON. I am an internist, but I have ended up having to get very familiar with all this.

If you listen to all the press reports, they loaded up at the beginning of the press report that IOM says this is fine. Then they go on and—at least the better coverage of what I saw of all this—to say that further research is recommended. I do not want to accuse the IOM of talking out of both sides of their mouth. They were in a very, very delicate situation.

I have some concerns about the way the study was passed through some of the reviewers, or some of the witnesses who have had a track record of being critical of this work. But I think we have a very serious issue here. You cannot refute a clinical and pathologic report with an epidemiologic study. You cannot do that. It is bad science. You have to fund an attempt to duplicate the clinical study and the pathologic study.

Would you agree with that?

Dr. HUMISTON. I am in agreement that the study should be replicated. I am in agreement that epidemiology alone does not refute.

What IOM reviewed was not just simply two or three articles. It was many.

Mr. WELDON. I know.

Dr. HUMISTON. And I did have the privilege of being in the room during the IOM report. So I was privileged to hear about changes in autistic brains of children in areas where the brain develops and is used for different things at different times. So the neuropathologist was describing how this could explain how we see regression.

There was one researcher there who showed how blood spots taken on the first day of life had different levels of vaso-active intestinal protein present in day 1 of children with autism, different levels than controls. I think IOM took Dr. Wakefield's hypothesis very seriously, as I think it deserved to be taken very seriously.

I also do not think that when you say in a light way that this is what you expected of IOM—I have great respect for those scientists. They came from many fields. And many of them did not come from vaccines.

So I think that taking that lightly is a disservice to those scientists and to the work of people who are moving forward with genetic explanations.

Mr. BURTON. We have to have a vote. We have 6 minutes left on the clock.

Mr. WELDON. I just want to clarify one thing.

You are accusing me of taking it lightly what they were doing. I do not like that at all. I consider this report a good report. I was pleased with the results of this report. But for them to spotlight and put the focus of public attention on the serious issues being raised about the safety of this vaccine by Dr. Wakefield, it is going to cause parents—just like it happened in England—to quit giving the vaccine. So they were in a very awkward situation, in my opinion.

I personally believe that there is a problem with this vaccine. And there is a subset of children who have a genetic predisposition to having problems with this vaccine. But further research is needed.

I do not want to be accused of taking their findings lightly. I consider this basically what they should have done. They did what was needed.

Mr. BURTON. Let me just conclude—and I hope you will come back for the third panel, Doctor, because I value your input.

Let me just say to you that they did send that report out for review to people from various pharmaceutical companies, and there were changes made, as I understand it, or corrections or perfections done on that report. I want to find out what those were.

Let me just ask two quick questions.

Does secretin cost $10,000 for two doses? I think my grandson got secretin and I know it did not cost that.

Dr. SCHNEIDER. There certainly are some practitioners who charge that much. That is absolutely true.

Dr. BRADSTREET. Mr. Chairman, $200 to $300 for what used to be available is no longer available is a fairly common cost to the physician. Relatively commonly, physicians double the price of something that they buy. So if they buy a vaccine for $20, they would like to sell it to the patient for $40. So that is an outrageous price.

Dr. SCHNEIDER. Our regular pediatrician would not give it us. We were trying to find any source.

Mr. BURTON. And my other question is, can chelation remove mercury from the brain?

Dr. BRADSTREET. There is no evidence of that at this point in time.

Mr. BURTON. Anybody else?

Dr. SEGAL. I agree. There is no evidence one way or the other. In fact, I spoke with two mercury experts. One suggests that mercury stays in the brain indefinitely. The other said that mercury is cleared within 50 or 75 days.

The bottom line is that nobody knows at this point.

Mr. BURTON. We need some research on that point as well.

Dr. SEGAL. Yes, we do.

Mr. BURTON. We will dismiss this panel. Thank you very, very much. We really appreciate it.

We would like to have your documentation and reports in total, if we can get those, so we can submit those to the health agencies.

Thank you very much.

We will be back. We will stand in recess to the fall of the gavel and go to our third panel as soon as we get back. It should be about 10 minutes.

[Recess.]

Mr. BURTON. We have a very large second panel. It is very, very important, though, that we cover all this territory. There will be other Members coming back from the floor in a minute.

[Witnesses sworn.]

Mr. BURTON. We will start with Dr. McDougle. You are recognized.

STATEMENTS OF CHRISTOPHER J. MCDOUGLE, M.D., RILEY CHILDREN'S HOSPITAL, INDIANA UNIVERSITY SCHOOL OF MEDICINE; ANDREW WAKEFIELD, M.D.; WALTER SPITZER, M.D., FACULTY OF MEDICINE, MCGILL UNIVERSITY, MONTREAL, CANADA; BOYD E. HALEY, DEPARTMENT OF CHEMISTRY, UNIVERSITY OF KENTUCKY; DAVID G. AMARAL, MIND INSTITUTE, UNIVERSITY OF CALIFORNIA, DAVIS; DR. ELIZABETH MILLER, PUBLIC HEALTH LABORATORY, ENGLAND; AND DR. MICHAEL D. GERSHON, DEPARTMENT OF ANATOMY AND CELL BIOLOGY, COLUMBIA UNIVERSITY

Dr. MCDOUGLE. Thank you very much, Chairman Burton and committee members. Thank you for the opportunity to come and speak with you today.

In addition, I would like to thank you personally for your recent efforts to assist our work in autism at the Riley Hospital for Children in Indianapolis. It is very much appreciated.

I was asked to come today to talk a bit about our current clinical, educational, and research activities at the Indiana University School of Medicine. I am currently the chairman of the Department of Psychiatry as well as the director of the section of child and adolescent psychiatry and the chief of the Autism/Pervasive Developmental Disorders Clinic.

I have been doing research and clinical care in the area of autism for the past 12 years or so. I came to Indiana in 1997, and at that point wanted to establish a formal autism clinic. At that time, we had approximately 100 children with a diagnosis of autism and other pervasive developmental disorders in our clinic. We brought those children together into a formalized manner and then began to build a clinical team.

At that time, I was the only child psychiatrist on the team and we had one clinic coordinator. We soon realized—once we got the word out that we had a formal clinic—that we needed to expand our clinical operation significantly.

We currently have an active clinic census of over 500 children. So in 3 years the census within the clinic has gone from 100 to 500. The disturbing and alarming part of that is that our waiting lists are out 9 months in advance now to bring children and families in for a new evaluation. So we have 9 months of people on the waiting list to even begin to get in to see us. At the same time, we are still trying to provide good care for the 600 current families within our clinic.

In an effort to meet some of these clinical demands, we have begun to hire additional faculty. I have added another full-time child psychiatrist, a nearly full-time behavior therapist, and a social worker to work with families to provide resources and help them with a number of the sticky issues they face.

Despite those additional clinical personnel, the waiting list persists. So I can certainly say firsthand that we are working very hard in Indiana. Autism is not rare. And we are having difficulty keeping up with the pace of personnel, despite adding additional personnel.

One problem with providing clinical care is that the reimbursement for such care is very poor. It becomes an issue as to how you are going to fund additional personnel to care for the growing population of your clinic when insurance reimbursement is often nothing or minimal. So that is an issue that I think needs to be addressed to a greater degree.

With regard to research, I am an expert in the area of psychopharmacology. I would say I am pretty good at diagnosing autism and related disorders and treating symptoms of autism that can become quite problematic. These symptoms—many of which have not been mentioned yet today—include aggression toward self, aggression toward others, property destruction, hyperactivity and inattention, interfering repetitive or ritualistic behavior, as well as the core disturbance of autism, which is a disturbance in the ability to relate appropriately to other people.

And we have a number of medicines we are studying in an effort to try to reduce some of these symptoms so that the child may be better able to participate in non-drug treatments, to be able to sit still and pay attention in speech therapy and other educational activities. But many times these symptoms I mentioned are so severe that the child cannot even get into a school or educational setting to benefit from these alternative treatments.

I would like to thank the National Institute of Mental Health. Approximately 3½ years ago they instituted a program to develop research units on pediatric psychopharmacology. They put out an RFA specifically to develop centers focused on autism. We were fortunate enough to be chosen as one of those centers in addition to four others across the country.

We recently completed our first study of a medication through this program with a medication called Risparidone, targeted really at some of the more severe symptoms of autism, including aggression, self-injury, and irritability. This was a double-blind, placebo-controlled study. We entered 101 children in adolescence into this study, which will make it by far and away the largest medication study ever conducted in autism to date by at least half—twice as large. So the idea of having multiple centers working together to get a larger sample size more quickly makes a lot of sense. I would like to see the RUPP networks continue to be funded.

In addition, we have begun to explore a number of what we call investigator-initiated studies. When we read the basic science literature, we get ideas about medicines or compounds that might be helpful for some of the symptoms of autism. We then go and try to generate some pilot data that if there is something to it we then apply for Federal funding. We have initiated a number of studies with some of those compounds.

The other areas of research in autism to date that I think are hopefully going to be fruitful include those that have been successful in investigating disorders in other areas of medicine over time, and that includes genetics. Certainly there have been large dollars put into the genetic research of autism to date without really significant results.

What that tells us is that this is a complex disorder, that there may be multiple genes involved in autism, and my guess is that eventually we may find in fact that multiple genes might be contributing to just certain small populations of autistic children. So it is going to be very difficult to pin down a gene or genes for autism, although clearly there is a genetic basis.

But I focus most of my energy on treating people that currently have autism. That has been emphasized today, not only the need to find the cause but to treat those people we already have with autism. I would like to see more funding put into treatment—not just drug treatment, but other forms of treatment—for autism.

The question came up earlier—and Dr. Segal referred it to me—regarding adults with autism. When I began my work 12 years ago at Yale University, at the time I was not a child psychiatrist. Due to various factors, I was not allowed to see children—maybe for a good reason. But I really wanted to study autism, so I initiated a clinic for adults with autism, which was really unheard of at the time.

My colleagues looked at me strangely and said, why would you want to study adults with autism? I asked them what they thought happened to children when they grew up. Most people view autism as a childhood disorder. In fact, it is a childhood-onset disorder that lasts forever.

Those individuals, in fact, are out there. One of my moonlighting jobs while I was in Connecticut as a consultant to the Department of Mental Health—and I actually went to the State hospital and the "back wards" where adults were hospitalized, and not infrequently could I identify individuals that had a history consistent with an earlier diagnosis of autism.

So they are out there, often misdiagnosed with schizophrenia or other disorders. But I will say that since I have been in Indiana and am now seeing kids, the ratio of kids coming to me versus adults is highly skewed in the direction of newer onset of cases in children. So the adults are out there, but there are many, many more kids and younger individuals who are being referred at this point. I have a sense that the numbers are increasing significantly. Again, I do not know the reason for that.

Mr. BURTON. Can you sum up, Doctor, so we get to some questions in just a few minutes?

Dr. MCDOUGLE. Sure.

I have really touched on our clinical and research efforts. The other thing I would like to highlight would be our efforts in education. That is something else that has been brought up today.

Pediatricians and family practitioners are not adequately educated about autism. I never heard about autism in medical school at all and first learned of it during my second year of psychiatric residency. So what we are doing within our clinic is having all the medical students in fact rotate through our clinic with us so that—we are the second largest medical school in the country—a large number of students are at least now seeing individuals with autism and being exposed to those treatments. I think that is important.

Mr. BURTON. Very good. I think we will come back and talk with you. You are doing a good job there and I am happy to work with you.

Dr. MCDOUGLE. Thank you.

Mr. BURTON. Dr. Wakefield.

Dr. WAKEFIELD. Thank you, Mr. Chairman. It is a great pleasure to be back here and provide you with an update and recommendations following last year's meeting.

[Slide presentation.]

Dr. WAKEFIELD. Let me just give you my terms of reference, and that is that we are dealing with a subset of children on the autistic spectrum. What I am going to present to you is based upon the scientific data. It is not fragmented. It is based upon a logical, hypothesis-testing framework. It is not anti-vaccine. However, it is not based upon assumptions of safety or coincidence. It is not an isolated opinion. It is the opinion of a growing number of physicians, as you have heard today, and it is based on conventional methods of listening to the patients and parents and the new-kid-on-the-block in this context is public health.

Let's go to the clinical history, which I will just briefly review, and that is of normal early development, of developmental regression, and the majority of parents cite the contemporaneous regression of their child following MMR vaccination. There is onset of associated neurological and gastrointestinal symptoms. The children also suffer recurrent infections.

You have heard that bowel symptoms are common in autistic spectrum disorder children, particularly in the United States, between 47 and 80 percent. So these findings may apply to a large proportion of the pediatric population with autism. The GI system are often masked by behavioral problems and if a history is not taken by an expert in gastroenterology, then these can be missed.

The question for the physician is, do these symptoms in these children reflect underlying intestinal disease? The medical profession hitherto have said, no, they do not. The answer is, yes, they do.

We have now published several papers, peer-reviewed papers. The first in the Lancet in 1988 and then in the American Journal of Gastroenterology in 2000, which was met with a very favorable commentary from the editor. And just a few weeks ago we published on the characteristics of this bowel disease in these children, comparing it with classical inflammatory bowel diseases, Crohn's Disease and enterocolitis, and normal controls, peer-reviewed and published data. We are presenting next week in Europe the discovery of not only a disease in the large intestine, but a disease in the small intestine as well.

And you have heard a great deal about autoimmunity. The disease in the intestine of these children is an autoimmune disease. There are antibodies in the blood of these children that bind to the lining of the bowel and seem to be part of an inflammatory reaction.

The key features are of developmental regression, swelling of the lymph glands in the bowel—this is consistent with a viral cause. The enterocolitis and inflammation throughout the gut is consistent with a viral cause. And the immunodeficiency we see in these children is consistent with a viral cause.

The important thing, though, Mr. Chairman, is that parents were right. The medical profession was wrong.

This issue of coincidence—and this is an important one—a child receives the MMR vaccine in the second year of life, and this is when the first signs of autism are noted. Bear in mind that we are dealing with regressive autism in these children, not of classical autism where the child is not right from the beginning. But coincidence is a situation you arrive at by due scientific and clinical investigation. It is not something that you assume from the outset. That is not good medicine; it is not bad medicine; it is nothing at all.

We will gain nothing from looking at children who had a single dose. But can we gain something from looking at children who had more than one dose? It is very important to raise this issue because this came up at the Institute of Medicine's review.

Here we have a group of children, each time line representing one child, and these children received not one dose but two doses of the MMR vaccine. What we see is that in many cases the red square and circle represent their contemporaneous regression into autism and subsequent deterioration. The green square and circle represent their first and second exposures to the vaccine.

What we see in many of these children is a double-hit phenomenon. They regress after the first dose, and then they regress further after the second dose. Let me give you an example, that is the child with the larger icons.

This child did not receive his first MMR vaccine until he was 4 years 3 months of age. This is not just recognition. He then deteriorated into autism. Clearly, this was not even autism by definition, a disintegrative disorder. He then received his second dose at 9 years of age and disintegrated catastrophically. He became incontinent, his feces and urine, and he lost all his residual skills. This is not coincidence.

The reason I am concerned about this, Mr. Chairman, is that at the IOM's review there was considerable concern and anxiety raised over these double-hit issues, these double-hit cases. The data were requested from me to be discussed in the closed session of the IOM, such were the concerns of the committee members. However, they find little or no mention whatsoever in the IOM's report.

The IOM's report gives one and a half pages coverage to Dr. Fombonne, who was one of the co-presenters. It was sent to him for review subsequently so that he could make amendments. It was not sent to me. It was also sent for review—as you pointed out—to people who have a clear conflict of interest in the vaccine arena.

The reason it was not sent to me, I am certain, Mr. Chairman, is that these cases were not included. This analysis was not included. And that gives me great cause of concern.

Let me read you a comment from the IOM's report. "However, well-documented reports of similar outcomes in response to an initial exposure to a vaccine and a repeat exposure to the same vaccine, referred to as challenge-rechallenge, would constitute strong evidence of an association." When we look at those, you see them. Those represent strong evidence of an association. They are well worked-up and well-characterized cases.

So the question is, is the virus present in the diseased intestine? These data were presented at the Cold Spring Harbor meeting earlier this year, and they were overseen by experts from the National Institutes of Health.

Is the virus present in the gut? Yes, it is. The viral gene and the protein are present.

Where is it located? It is located in the specific cells that we would recognize if it were the cause of this disease.

How much is there? It is certainly a low-level infection.

Can we confirm the presence of the virus with different technologies? Yes. We have now applied 10 different technologies to this.

Does the presence of the virus distinguish these children with autism from controls? It is present in 93 percent of the children with autism and 11 percent of controls.

And can it be confirmed in independent laboratories? Bearing in mind that Professor O'Leary's laboratory was completely independent from mine initially, these further studies are underway, and the answer provisionally is yes.

The question we have now, Mr. Chairman, is, what is doing there? We are not saying it is the cause of this regressive autism, but the question is, what is it doing there? That is the next phase of our logical progression.

What is the link between the gut and the brain? We do not know, but it certainly is biologically plausible that one exists. It may be that it is an autoimmune process shared by the gut and the brain, or it may be that there are toxic contents of the gut that are getting through and hitting the brain in a situation similar to that which we see in patients with chronic liver disease.

Here is a child whose only treatments have been to the gut. He is an autistic child whose only treatments have been diet and control of his gastrointestinal inflammation. You can see that by solely treating the gut there is a demonstrable improvement.

What about the shortcomings in epidemiology? In short, Mr. Chairman, they have tested the wrong hypothesis. My colleagues and I have not proposed any hypothesis thus far that can be tested by epidemiology. We are still in the process of defining the parameters of this disease. In particular, we are concerned with what makes a child potentially vulnerable to a subsequent adverse outcome to an MMR vaccine. What sets the child up to then respond adversely to the vaccine?

What I have done is spent the last 3 years traveling the world and interviewing patients in our own clinic to try and establish from the clinical histories what those vulnerability factors might be. When we look, we see that there is a strong family history of autoimmune disease, particularly on the mother's side—of diabetes, thyroid disease, or Crohn's Disease, for example—that the child receives the vaccine in the presence of an infection or in the presence of recent or current antibiotic use, that the child has preexisting allergies, particularly food and milk allergies, and that the child receives many vaccines at the same time.

These are consistent elements that have emerged in the clinical histories that I now believe may represent vulnerability factors.

So let's look at what the data show. The hypothesis that has been tested and put down to me—which has nothing to do with me, whatsoever—is that if this is related to MMR vaccine, then at the point of introduction of the vaccine there should have been a step-up in the numbers that should have levelled out as the vaccine uptake was saturated.

Is that a reasonable hypothesis? Can we assume that the background susceptibility of the pediatric population has remained constant? No, I do not. I do not think we can do that. What we actually see is an increasing incidence.

The time trend analysis for autism in the United Kingdom and California have confirmed the rise. The data are entirely consistent with an increasing vulnerability of infants to adverse reaction to an MMR vaccine. They are certainly consistent with the clinical histories of affected children. And again, I am not saying that this in any way proves causation. What I am saying is that we will gain insight into this disease from taking appropriate clinical histories and investigating and set up our epidemiologic hypothesis based upon that. Now we have a hypothesis that can be tested.

So in conclusion, Mr. Chairman, there is a group of children whose autism is associated with developmental regression, immunological abnormalities, intestinal disease, persistence of measles virus infection in the intestine, and onset following MMR vaccination. What I would recommend is that there be a high-level strategic meeting that is formed and a working group formed under the American Gastroenterological Association to investigate this specific group of children with the aim of providing appropriate and necessary clinical care for these children.

That is an absolute priority. The medical profession has let them down very, very badly thus far. And a research strategy needs to be defined by this group in order to understand this disease.

There needs to be immediate institution of active surveillance for vaccine-related adverse events. Passive surveillance has known to have failed. I believe that monovalent vaccines should be made available. This should be an issue of parental choice. I think it should be a priority that we identify those vulnerability factors—for example, a child who might be on antibiotics—and exclude them from vaccination until they have improved. We also need a policy for identifying and protecting susceptible children, and most importantly thereafter, informed choice.

It is ultimately a pro-vaccine argument, Mr. Chairman. If we have the ability with a single vaccine to prevent not only the acute disease, but this concurrent exposure, then we have the ability to protect children both against measles, mumps, rubella, and against this devastating consequence.

Thank you.

[The prepared statement of Dr. Wakefield follows:]

TESTIMOMY TO THE CONGRESSIONAL OVERSIGHT COMMITTEE ON GOVERNMENT REFORM

Dr Andrew J Wakefield MB BS FRCS

Introduction

Mr Chairman and members of the Committee, I are here to review the progress in our understanding of the possible association between childhood developmental disorders, gastrointestinal disease and vaccines, and to make certain recommendations.

This area of inquiry is beset with issues that go way beyond the clinical and scientific evaluation and treatment of affected children; implications for Public Health policy are far reaching and demand an early resolution to the issue of whether or not there is a causal relationship between MMR vaccine - the focus of my own particular inquiries - and childhood autistic spectrum disorder (ASD).

I consider many of the associated issues, including attacks on personal integrity, peripheral and will not address them here. Rather, it is my wish to bring the Committee up to date with the clinical science, and to try and offer a **positive and achievable strategy** for addressing the important issues, for the sake of affected children and for the protection of future generations.

I have spent the last 36 months travelling widely, and studying the subject in some depth, in order to broaden my own understanding of the many aspects of the current dilemma. My starting point, as is the starting point for much of medical science, is with the clinical histories of the individual children. These have been an essential element in my own understanding of the issues. Having reviewed a large number of these histories it is only now that I am in a position to propose hypotheses that are capable of being examined by epidemiological methods. Some of the factors, relevant to the hypotheses, will be set out later in this written testimony.

I will start by bringing the Committee up to date with the research findings.

Progress

At the last congressional hearing, Professor J. O'Leary and I presented results of a detailed analysis of the clinical and pathological features, and early virological findings, in a group of 60 children with regressive autism.

These original data, and subsequent investigations confirm that there is a group of children with autism in whom there is a consistent and characteristic pattern of pathology in the gastrointestinal tract. This pathology consists of lymphoid nodular hyperplasia (swelling of lymph glands) in the terminal ileum and large intestine (colon), and inflammation in the mucosal lining of the intestine.

The initial report describing this possible new syndrome of regressive autism and intestinal inflammation was published in the *Lancet* 1998[1]. The data describing the first 60 children, comparing them with appropriate controls, were published subsequently in the *American Journal of Gastroenterology*[2]. We have now investigated nearly 200 affected children, and continue to detect the same pathological findings in the intestine. The recognition of this syndrome is rapidly gaining wider acceptance among Gastroenterologists. In an editorial accompanying the second paper[2], the Editor of the *American Journal of Gastroenterology* wrote:

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[1] Wakefield, A.J., et al Lancet 1998;351:673-641

[2] Wakefield, A.J., et al Am J Gastroenterol 2000;95:2285-2295

"[the authors] are to be congratulated on opening yet another window onto the ever-broadening spectrum of gut-brain interactions. Their findings raise many challenging questions that should provoke further much-needed research in this area, research that may provide true grounds for optimism for affected patients and their families."[3]

Professor Eamon M.M.Quigley
Dept of Medicine, National University of Ireland, Cork

A subsequent detailed analysis of the immune characteristics of the mucosal lesion in the large intestine (colon) was published recently in the *Journal of Pediatrics*[4]. This study confirmed the presence of an apparently novel form of immune-mediated inflammatory bowel disease in children with ASD. The intestinal findings were not seen in developmentally normal children. The data are consistent with increasing evidence for damage and dysfunction of the lining of the bowel (epithelium) in this cohort of children. The paper concludes that: **"the increasing evidence of immunopathology [in children with autism] suggests that focus on autoimmunity, rather than genetics, may have now become a priority."**

In a highly supportive editorial comment, the Editor of *The Journal of Pediatrics* concluded:

"This **[the study findings]** ***seems to point to gut epithelial dysfunction leading to altered permeability and subsequent entry of "CNS altering substances." It follows that treating the gut disease may affect the CNS disease.***

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[3] Quigley, M.M., Am J Gastroenterol 2000;95:2154-2145
[4] Furlano, R. et al., Journal of Pediatrics 2001;138:366-372

Journal of Pediatrics March 2001.

Editorial Comment.- William F Balistreri MD.

The small intestinal lesion

Similar detailed investigations of the small intestinal mucosa in these children has confirmed the presence of an immune pathology, characterised by infiltration of the epithelial lining by CD8+ lymphocytes, structural damage to the epithelium and binding of serum antibodies to the epithelial membrane.[5] [6] These observations distinguish the children with autism from healthy paediatric controls and those with alternative inflammatory pathology, such as, coeliac disease. The findings are consistent with an autoimmune disease of the intestine, and are similar to the autoimmune intestinal disease seen in some patients with AIDS.

Horvath and colleagues, from the University of Maryland Medical School have published clear evidence of upper gastrointestinal (i.e. esophagus, stomach and duodenum) disease in the majority of autistic children presenting with gastrointestinal symptoms[7]. Their findings include inflammation of the esophagus, stomach and duodenum, with associated deficiencies in the digestive enzymes that are normally produced in the small intestinal epithelium. Based upon similar symptoms in children under our care, and the findings of Horvath et al, we have included a similar endoscopic evaluation of symptomatic children and have confirmed the high prevalence of inflammatory pathology in these areas, consistent with Horvath's findings (manuscript in preparation).

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[5] Torrente, F. et al., Journal of Paediatrics, Gastroenterology and Nutrition. 2000;31 (Suppl 2) A546 (manuscript in preparation)

[6] Wakefield, A.J. & Murch, S.H., Molecular Psychiatry (In press)

[7] Horvath, K. et al., Journal of Pediatrics 1999;135:559-563

The gut-brain connection One outstanding question applies to the nature of the link between the disease in the diseased intestine and the developmental and behavioural problems in affected children. A manuscript is appended to this testimony, that elaborates the evidence for a **toxic gut brain-interaction** in this subset of children, providing a biologically plausible - and testable - mechanism for how a primary intestinal pathology might lead to neurological damage[8]. It is acknowledged, that in view of the immune disorders evident in these children, there may well be an autoimmune damage to structures within the developing brain, and this possibility is under investigation. Toxic and immune-mediated cerebral pathologies are by no means mutually exclusive. Included in the appended manuscript is reference to two further papers that have been published in the last several years which have a direct bearing on our growing understanding of the role of the gut in developmental disorders, including regressive autism. Bolte has proposed a role for the toxic products of certain species of bacteria in the intestine, in mediating the encephalopathy that is associated with behavioural disturbances in affected children[9]. This situation would be analogous to the encephalopathy that is seen in patients with acute or chronic liver failure, where toxic bacterial metabolites are absorbed into the bloodstream from the gut but not removed by the liver, resulting in characteristic encephalopathic changes in the patient. In seeking to test Bolte's hypothesis, Sandler et al conducted an open-label study of oral antibiotic (Vancomycin) therapy in children with autism[10]. Vancomycin is an antibiotic that is not absorbed from the gut. The authors demonstrated a clear cognitive improvement in children during the treatment period. Children deteriorated behaviourally following cessation of Vancomycin therapy, suggesting that the aberrant effects of the intestinal bacteria were likely to be the consequence of an underlying intestinal abnormality, as indicated by our own studies, but that the products of these bacteria play an important role in mediating the gut-brain interaction and associated behavioural pathology.

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[8] Wakefield, A.J.et al., Entero-colonic encephalopathy, autsim and opioid receptor ligands (in preparation)

In summary, there is growing evidence that toxic products from the diet and intestinal bacteria leak through the damaged bowel and injure the developing brain.

Nonetheless, the studies of Bolte and Sandler provide an important insight into a possible mechanism of gut-brain interaction that is likely to be important in these children with regressive autism.

To what proportion of autistic children is the finding of gastrointestinal disease relevant? From independent sources, both Melmed et al[11], and Horvath et al[12] have shown that gastrointestinal symptoms are common in children with autism compared with developmentally normal controls. The symptoms described by these authors mirror those in children seen in our clinic and are, we believe, likely to reflect identical pathology. Further studies of autistic children who have no overt gastrointestinal symptoms indicate underling intestinal pathology[13]. **These children may possess the intestinal pathology that affects the brain but do not demonstrate sufficient symptoms to be clinically significant or alert a parent to the problem**. These observations are reminiscent of celiac disease, an allergic sensitivity to dietary gluten, where a large proportion of cases may be subclinical, and are only detected by population screening. This phenomenon is known as the ***"celiac iceberg"***.

It is vitally important to recognise this phenomenon since those with subclinical celiac disease are at risk of long-term complications unless appropriate therapy is instituted. It is highly likely that a similar *iceberg* effect is operating in children

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[9] Bolte, E.J., Medical Hypotheses 1998;51:133-144

[10] Sandler, R. et al., Journal of Child Neurology 2000;15:429-435

[11] Melmed, R. et al., Journal of Paediatric Gastroenterology and Nutrition. 2000;31 (suppl 2) A116

[12] Horvath, K. et al., (in press)

[13] D'Eufemia et al., Acta Paedtatrica 1996;85:1076-1079

with autism, and that there may be either a primary, or associated intestinal pathology in many affected children.

Since last years' Congressional hearing last year a number of meetings have taken place in the U.S. to consider the issues. The first was June 2000 at the American Academy of Pediatrics. Due to the unavailability of invitees from the CDC the original meeting was rescheduled for a date that made it impossible for Professor O'Leary and I to attend. The deliberations of this meeting have yet to be published.

The second significant meeting was convened by Dr. Ian Lipkin of the Emerging Pathogens Laboratory, University of California, Irvine. This meeting took place February 2001 at Cold Spring Harbour and was, for the most part, extremely constructive. The organisers are to be commended on this initiative. At this meeting confirmation of the detection of measles virus in the intestine of children with ASD was endorsed (see below). The proceedings of this meeting are due to be published as part of a series of invited articles in *Molecular Psychiatry*. It was confirmed that independent virological studies of affected children, focusing on the detection of measles virus predominantly in circulating immune cells, were planned. I strongly encouraged the testing of intestinal biopsy samples in addition to blood samples, since viral detection is likely to be more successful.

The third meeting, convened as a direct consequence of a request from this Committee, took place at the National Academy of Sciences, Institute of Medicine in March 2001. Presentation of the deliberations of this Committee are due to be reported this week. Unfortunately, due to the presence of the press, virological data undergoing peer review, could not be presented, which largely defeated the purpose of the meeting.

Summary

In summary, primary intestinal pathology may be a significant part of the disease process in a large, but as yet, undefined proportion of the children with autism. In the great majority of autistic children who have been investigated appropriately, according to their intestinal symptoms, there is inflammatory pathology the features of which are consistent with an autoimmune mucosal lesion in both the large and small intestine. We propose that this is intestinal disease makes a major contribution to the developmental/behavioural pathology in affected children. The findings, in these ASD children, of an autoimmune intestinal disease, associated intestinal lymphoid hyperplasia, and immunodeficiency, are consistent with a viral cause for this syndrome.

Recommendations

1. Based upon the peer reviewed medical and scientific literature, children with developmental disorders and gastrointestinal symptoms should be thoroughly investigated for underlying intestinal pathology, according to the principles of **evidence-based medicine**. The associated intestinal pathology is amenable to therapy and merits active treatment.

    - These children deserve investigation to rule in or rule out organic immune and intestinal pathology
    - Only with investigation and diagnosis can appropriate therapy be instituted
    - Because of their behavioural diagnosis, these children are often denied access to appropriate healthcare. It is evident that for many children, their intestinal and other physical symptoms are put down to their behavioural problem, and are not being investigated appropriately. This situation must not be allowed to continue.

- To exclude these children from appropriately resourced medical intervention is discriminatory and unacceptable. Indeed, any such discriminatory policy may actively prejudice the perception of health care providers and make them reluctant to institute necessary medical investigations and treatment of these children.

2. That **investigation of intestinal symptoms** - hitherto largely ignored in children with developmental disorders - should be given high priority, and that the identification of **screening tools** to identify autistic children with **subclinical intestinal disease** are given a similarly high priority.

3. That, consistent with the IOM's recommendations published this week, structured, multidisciplinary gastrointestinal, immunological microbiological and neurodevelopmental research programmes should be initiated between collaborating institutions.

4. That, in order to institute points 1-3. above, a high level strategic meeting be called, and a **working group** established, under the auspices of the **American Gastroenterological Association**, to include members of the American professional societies for Microbiology, Immunology, Pediatrics, Neurology and, in addition, Autism speciality groups such as DAN (Defeat Autism Now).

5. That this meeting should seek to define a strategy for:

- clinical investigation and management of affected children;

- application of our extensive knowledge in the respective areas of inflammatory bowel disease, intestinal motility disorders, mucosal immunology, intestinal microbiology, nutrition, food allergy toxicology, and neuroimaging, to the study of the gut-brain-immune axis in affected children.

6. That the **working group** should strive to develop (l) a management guide for clinicians and (2) set priorities for clinical and basic scientific investigation.

My colleagues and I would be happy to help co-ordinate such a meeting and to nominate names of possible members of the working group whose contribution I would see as essential for its success.

Virology

The majority of parents seen in our clinic and many parents of similarly autistic children throughout the developed world cite exposure of the MMR vaccine as the trigger for regression in their previously normal child. For many reasons, not least of which are the benefits of vaccination, clinicians and scientists have been unwilling to entertain the possibility of a causal relationship.

The identification of an immune mediated intestinal pathology has provided a focus for investigation of this possibility. Specifically, we have tested the hypothesis that measles virus (or elements thereof) should be detectable in the enlarged lymph nodes in the ileum. We have now completed a preliminary series of studies which sought to answer the following questions:

- Is measles virus present in the intestinal tissues of affected children and specifically, can measles virus protein and genetic material be detected in the same location?
- If measles is detected where is it located? Specifically is it present in the swollen ileal lymph nodes?
- How much virus is there?
- Can the virus be sequenced in order to characterise the strain of the virus present?
- Can the results be confirmed by different technologies?
- Does the presence of the measles virus distinguish autistic children from controls?
- Can the results be confirmed in independent laboratories?

In a coded-blinded study using appropriate positive and negative controls these questions have largely been answered. The data are not presented here, since this may prejudice the process of peer review and publication. However, it is possible to confirm that:

- Both measles virus gene and protein are present in intestinal tissues from a majority (93%) of autistic children studied. A variety of different measles virus genes were detected
- The virus is present in the reactive lymph nodes.
- The virus is present in specific cells that would make it a likely cause for the lymph node reaction. Other common childhood viruses including adenovirus, herpes virus, mumps, rubella and HIV were not present.
- The virus was present in relatively small amounts, making the application of highly sensitive molecular detection techniques an essential component of these studies.
- Viral sequencing confirms the presence of measles virus. Strain-specific sequencing studies (i.e. to discriminate wild and vaccine strains) are currently under way.
- Overall ten different techniques have been applied to detect measles virus in these biopsies, with all reporting positive results
- There is a highly statistically significant difference between cases and controls for the presence of measles virus in ileal biopsies. It is notable that measles virus was present in a small percentage (11%) of biopsies from developmentally normal children.

These data are due to be presented at Digestive Diseases Week, Atlanta, GA, May 2001.

Collaborative studies with independent laboratories are being undertaken in order to assess the reproducibility of these findings. An invitation has been extended to members of the CDC to spend time in the laboratory of Professor O'Leary in order to participate in the analysis of tissue. In addition, independent studies analysing in intestinal biopsies from children in Canada and the United States have been prompted by these investigations.

Part of my efforts over the last 24 months have been to encourage and initiate some of these studies. At the recent Cold Spring Harbour meeting on Autism and Environmental Agents it was the expert's conclusion that the evidence confirmed the presence of measles virus in intestinal biopses from children with ASD. It is important to note that the data identify an association only; the presence of the virus does not make it the cause of the autistic regression. Whether or not this is the case will only be determined by further study. Once again, the virology data are consistent with, but not proof of a causal association between measles virus and the intestinal disease in children with ASD, and in view of the plausibility of the gut-brain scenario described above, the data are also consistent with - but not proof of - measles virus causing both intestinal disease and autistic regression in these children.

The findings move the arguments to a new level that have implications for public health policy. Rather than having parental reports alone, of a temporal association between MMR exposure and developmental regression, there is now definitive evidence of an novel and specific pathology in the intestine of children with ASD that is associated with the presence of measles virus. In association with the findings of Kawashima et al, of measles virus in the peripheral blood of some children with ASD, it is no longer an correct or acceptable to state that there is no evidence of an association between MMR and this syndrome. In light of this and in view of the acknowledged lack of adequate safety studies on the MMR vaccine[14] the case for making MMR vaccination either mandatory, or the exclusive mode of protection against measles, mumps and rubella is, in my opinion, difficult to justify. Parents should be given an informed choice of vaccination strategy, including the provision of single vaccines. I fully endorse the need to continue to protect children against these infectious diseases.

At present we are performing strain-specific sequencing on the virus to determine whether the virus in the intestine of these ASD children it is a vaccine or 'wild type' (natural) strain. The current teaching is that there is no evidence for persistent infection with the vaccine strain virus. It must be assumed that this would be an undesirable consequence of vaccination in view of the association between persistent infection and delayed severe neurological disease.

Vaccination is the only recorded exposure these children have to measles, and wild measles has not been circulating within their lifetime. However, it could be that the vaccine failed to protect them from (and may, in fact, have predisposed them to) a covert atypical natural measles infection. There are both clinical and experimental data demonstrating that failure of a measles vaccine to produce adequate immunity may actually predispose to immune disease upon re-exposure to measles virus.

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[14] Grune and Stratton IOM

Alternatively, the presence of the virus may represent innocuous carriage, although I consider it would be imprudent to make this assumption in the face of the immune and pathological data, prior to thorough investigation.

Clear priorities must be, to:

- conclude the strain-specific sequencing studies,
- conduct investigations of measles-specific immune responses in affected children and appropriate controls.
- fund independent virological studies.
- include the development of a strategy for the conduct of viral studies in the remit of the **working group** as outlined above.

Review of MMR vaccine safety

In early 2001 Dr Montgomery and I published a critical review of pre-licensing studies of MMR safety[15] (the bibliography for this section is included in reference 16). In this review we raised substantial concerns over the inadequacy of these safety trials, in terms of the numbers of individuals studied, the lack of appropriate control groups, and the lack of any long term safety evaluation. In particular, we raised concerns over the use of combination of live viruses in the MMR vaccine. These concerns were endorsed by the peer reviewers, whose comments were published alongside the review.

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[15] Wakefield, A.J. and Montgomery, S.H., Adverse Drug reactions & Toxicology Review. 2000;19:265-283

This review has been criticised as being inaccurate and selective in certain respects. We readily acknowledge the omission of one substantial paper. This was not due to deliberate selection, but due to failure to identify the study in our literature search. This omission was a study of twins from Sweden receiving MMR vaccine. The study was well designed, although it sought to detect adverse events occurring only within three weeks of vaccination. Despite its omission, this study involved far too short a period for the adequate evaluation of safety, and we do not believe that it mitigates against the concerns raised in our review. We reject other criticisms as inaccurate and misrepresentative of the substance of our review[16].

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[16] For example, we presented a re-analyses of the adverse reactions data in the original studies of MMR by Stokes 1971. Our paper was concerned with issues of safety and we presented a reanalysis of the safety data. Stokes' paper quotes vaccine administration to larger numbers of children for whom safety data are not provided and for whom, therefore, reanalysis was not possible.

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Viral "interference"

In the review, particular concerns were raised in relation to the potential for "interference" between the component viruses of MMR. This phenomenon, which is universally recognised by virologists, refers to the influence of one virus upon another when they are encountered by the host concurrently, or in close temporal sequence. The way in which one virus interferes with another is not fully understood; however, a substantial component of this interference is through an influence of one virus upon the immune systems' ability to deal effectively with another virus. In human disease viral interference may profoundly and adversely affect the nature and outcome of a patient's disease.

Therefore, a major safety consideration in the context of polyvalent vaccines such as MMR, is the potential for adverse interactions between the component live viruses, particularly in view of the immunosuppressive properties of measles virus. In addition to the elements of unnatural age, route, dose, and strain of infectious exposure, the childhood immune system must cope with a combination of viruses that it would have been extremely unlikely to encounter under circumstances of natural exposure. In an executive summary, members of the IOM's Vaccine Safety Committee, reiterated this anxiety in the context of virus-induced immunosuppression and polyvalent vaccines. They stated:

"It may be asked, then, whether the use of combination viral vaccines might exacerbate the potential problem of immune suppression. The committee found no report of a systematic comparison of the effects of monovalent and polyvalent live attenuated vaccines on immunity".

In 1995 concerns over the potential for interference between the components of vaccines were raised again at a meeting of US vaccine officials. Specifically, Belshe (St Louis) stated that:

"To be confident that a particular vaccine had no effect on another vaccine given simultaneously, comparative studies should be performed".

Halsey (Johns Hopkins) considered that such studies would be both *"too large"* and *"unnecessary"*. Halsey conceded, however, that: *"If there is a biological reason to suspect that there may be interference or blunting or blocking, then comparative studies should be done."*

Is there a "biological reason" to suspect that "interference" may occur between the component viruses of MMR? It is evident from the medical literature prior to 1977, that the outcome from measles infection may be influenced by close temporal exposure to another virus. A close temporal exposure to measles virus and another infection, for example, chickenpox or certain enterovirus infections, is associated with an excess risk for delayed encephalitis. With respect to possible adverse events that are currently topical, atypical patterns of exposure to measles, mumps, rubella and chickenpox have been associated with both autism and, for measles virus, developmental regression. *In utero* and infant exposures have been identified as periods of apparent susceptibility, when both the brain and the immune system are undergoing rapid development. It is notable that a close temporal relationship in the exposure to more than one of these infections during periods of susceptibility, may compound both the risk and severity of autism. Similarly, atypical patterns of measles infection, including a close temporal exposure to mumps infection, but not other common childhood infections, have been identified as a significant risk factor for classical inflammatory bowel disease, Crohn's disease and ulcerative colitis.

Clues that the component viruses of MMR could interfere, one with another, were provided in the very first pilot studies of this vaccine. In 1969, Buynak et al sought to examine the effects, in humans, of various combinations of measles, mumps and rubella strains. In addition to seroconversion (viral antibody production), clinical end-points included the comparative frequency of measles rash and fever.

The authors demonstrated clear evidence of dose- and strain-dependent interference between the component viruses in the MMR vaccine. However, despite the potential implications for safety the matter was not followed up by these authors.

Six years after Buynak's study, in 1974, the potential for interference in MMR was subject to a more detailed follow up of the original observations, by Minekawa et al. The most striking observation was of a dose-dependent influence of the mumps vaccine upon not only clinical reactions to the measles component, but also seroconversion to rubella vaccine. This same pattern of interference was also indicated by the study of Eddes et al that compared clinical reactions to monovalent measles and MMR vaccines.

The ability of mumps virus to interfere with the cellular immune response to measles virus and, thereby, to potentially impair viral clearance and increase the risk of persistent infection and/or initiate autoimmune disease, is a real and worrying possibiilty to some of those involved in the current debate. The contemporaneous interpretation of Minekawa et al was that further studies were necessary. From the published literature it does not appear that any further studies were undertaken.

Further evidence of viral interference – in this instance, between the measles and rubella vaccines – comes from Crawford and Gremillion's study of U.S. Airforce recruits in 1981. In a relatively large prospective study, safety and efficacy of measles and rubella vaccines (given either alone or in combination) were compared with unvaccinated controls. Five hundred and twelve vaccinees were compared with 835 unvaccinated controls and data were stratified by sex. The authors noted an increase in reports of fever and diarrhoea in those immunized with both vaccines simultaneously. In women there was an increase in complaints of myalgia (muscle pain) after simultaneous immunisation. The data merit more detailed consideration; in recruits receiving either monovalent measles or rubella vaccines there was no significant increase in diarrhoea compared with unvaccinated controls (measles vaccinees versus controls [men] OR 2.51; CI 0.06-9.99) and [women] OR 3.61; CI 0.26-50.42; $p>0.5$; Odds ratios for rubella vaccinees versus controls cannot be calculated since no men or women reported diarrhoea after rubella vaccine alone. In contrast, compared with unvaccinated controls there was a significantly increased risk of diarrhoea following simultaneous measles and rubella vaccination in both men (OR 7.31; CI 1.11-34.64) $p<0.001$) and women (OR 17.29; CI 1.14-247.09; $p<0.001$). For gastrointestinal adverse events (diarrhoea), the effect of simultaneous measles and rubella vaccination is not additive but apparently synergistic (compound). These findings were obvious to the authors and were remarked upon in the results. In the jargon of vaccine regulators, **a signal had been generated**, but it appears to have been ignored.

Indications that novel adverse events might be associated with the combined MMR vaccine, rather than the monovalent component vaccines, have come from Plesner et al's study of gait disturbance following MMR in Denmark. Several prior studies had indicated that gait disturbance (ataxia) might occur in up to 1 in 1000-4000 recipients of MMR. In Denmark this association had not been detected with any other vaccine administered to children of the same age, prior to the introduction of MMR in 1987. In a recent follow up of the mandatory passive reporting system operated in Denmark, Plesner not only confirmed this association but also indicated that the more severe ataxias following MMR may be associated with **residual cognitive deficits in some children**. This association is specifically relevant to the debate on MMR and autism, as parents of autistic children who suspect a link with MMR, not infrequently report gait disturbances.

Vaccine manufacturers recognise that the problem of interference exists, but appear to have regarded it as more of an inconvenience that a safety concern. Douglas of Merck stated recently:

"The complexity of vaccine delivery today in clinical practice with 15-17 injections in the first two years of life emphasizes the need for development of combination pediatric vaccines, for example, putting DTaP, HBV, HIB and IPV together. This has proved to be far more difficult than previously believed due to unpredicted immune interference and incompatibilities on mixing of different components, demonstrating again the inadequacy of our understanding of how vaccines work and the empiric nature of the science."

Why, however, in spite of evidence provided by studies undertaken two decades earlier, should such interference be considered "unpredictable" and, indeed, remain unstudied?

In summary, the data indicate that the combined MMR may be associated with novel adverse events (i.e. not seen with the single vaccines) including regressive autism. These novel adverse events may arise because of the interaction of the viruses (with each other and/or with the immune system) that leads to an increased risk of autoimmune disease. Knowledge of viral interference in MMR has been available for over 30 years but has never been adequately studied.

Shortcomings in current epidemiology

Currently available epidemiological studies are inadequate to rule in or rule out a causal relationship between MMR and ASD. Several recent epidemiological studies have sought to examine this association[17] [18]. Description of the details of these studies will be left to expert witnesses. These studies have involved the analysis of time trends in the incidence[22] or case load[21] of autism in defined populations (UK and California). These studies sought to examine whether there was any correlation between the dramatic increase in new cases of autism (which was confirmed) and MMR vaccine uptake. In their analyses no correlation was found. These studies have been portrayed by some as testing the 'Wakefield Hypothesis'. **Categorically, this is not the case and any such interpretation would be wholly inappropriate.**

I will attempt to clarify this statement. The work of my group and our collaborators colleagues has been concerned with the identification and description of an apparently novel disease complex in children. In the context of this disease we have not yet described or proposed any hypothesis that is testable in an epidemiological context. We are only just beginning to understand the complex nature and clinical characteristics of the syndrome. As such, we are not yet in a position to provide a comprehensive case-definition. Of particular relevance to the design of epidemiological studies, we have been concerned to identify any **vulnerability factors** that might put a child at increased risk of developmental regression following MMR vaccination.

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[17] Kaye, J. A. et al., BMJ2001;322:0-2
[18] Dales, L. et al., JAMA2001;285:1183-1185

My colleagues and I have now taken detailed clinical histories from parents of over 250 affected children in our own clinic, and I have travelled extensively in the last 3 years for the purpose of listening to clinical histories from parents and health care providers across the United States, Canada, and Europe in order to assimilate these histories and to compare them with our own experience.

In particular, the clinical histories have identified the following circumstances that are frequently associated with the receipt of the MMR vaccine, by parents of affected children. These include MMR vaccination of a child who:

- has an current infection (e.g. ear or upper respiratory tract infection
- is either receiving antibiotics, or is vaccinated shortly after a course of antibiotics;
- has a history of atopy (allergy), particularly milk allergy;
- has received multiple vaccines concurrently;
- has a strong family history of autoimmune disease; and,
- in light of the critical observations reported by Dr F. Yazbak, a maternal history of MMR/rubella vaccination immediately prior to pregnancy, during pregnancy, or during the period of post-partum nursing.

These clinical associations may represent co-factors for, or makers of, a susceptibility to an adverse reaction to MMR vaccine, and specifically the syndrome described above. The identification of these potential co-factors allows us to predict what the effect of the combination of MMR plus such co-factors would be, over time, at the population level, if MMR were causally related to ASD. We would hypothesise that:

- following the introduction of MMR there would be an increase in the incidence of autism from previous baseline levels;

- that the background vulnerability for ASD following MMR would increase in successive birth cohorts (groups) as the rate exposure to these co-factors - infant allergy, maternal autoimmune disease, infant antibiotic use and additional vaccine (including the associated preservatives and adjuvants) administration - increased over time. The increase in all of these potential co-factors has been clearly documented. The issue of antibiotics and novel vaccines is particularly important in this respect, since these may exert potent influences on the developing immune system and it is biologically plausible that they may render the infant less able to handle a live viral vaccine given either at the same time or subsequently.
- That, in view of the high uptake of MMR and the concomitant increase over the last 2 decades in infant exposure to potential co-factors, the incidence of autism would continue to rise beyond the introduction and widespread use of the MMR vaccine.

It is important to note that this hypothesis has been arrived at independently, following a detailed examination of the clinical histories of affected children, and an assessment of the biological plausibility of the sequence of immune and pathological events. It has not been influenced by the publications of either Kaye et al[20] or Dales at al[21] , although **their findings are consistent with, and strongly supportive of, this hypothesis.** It is my impression that the trend in autism incidence is wholly consistent with a causal relationship with the MMR vaccine at the population level.

For the sake of completeness I have included, in **non-lay terminology** a summary of the current hypothesis for the origins of the syndrome in this cohort of children with autism.

Hypothesis

For the cohort of children with regressive autism – a group that, we believe, may account for a large proportion of new diagnoses – we hypothesise that the root problem is in aberrant early immune programming, particularly within the mucosal immune system. Within the last decade there has been substantial increase in allergies of all kinds, particularly dietary, which may result from recent dramatic changes in the pattern of infant environmental exposures. There are increasingly explicit links between mucosal infectious exposures and the establishment and maintenance of mucosal immune tolerance. The natural trajectory over time, from a T_H2 dominant foetal/neonatal immune response to a balanced T_H2/T_H1 responsiveness that likely reflects healthy immunological maturity, may permit the generation of appropriate cytotoxicity in the face of viral exposures. Factors that modify this transition in T helper cell effector function, including vaccines, toxins or natural infections, may prolong T_H2 skewing, and thus impair antiviral responses. Inappropriate early conditioning of the mucosal immune system, for which the faecal flora plays an obligatory role, may allow inappropriate persistence of agents which home to gut-associated lymphoid tissue. The immunomodulatory nature of MV suggests that persistent expression within mucosal lymphoid tissue may affect mucosal tolerance mechanisms, in particular inducing T_H2-skewing through mechanisms including inhibition of dendritic cell IL-12 production.

If it is the case that MMR vaccine is causally related to this syndrome – a case as yet unproven - **it should not be assumed that the associated risk remains static within any given population over time**. The rapid increase in numbers of children with dietary allergy, itself associated with reduced CD8 cell numbers, prolonged viral infections and familial autoimmunity, suggests that the numbers of children who may be at risk of aberrant responses to infectious agents will have risen in the last decades. Potentially relevant overlap, in which ubiquitous infectious exposure is followed in a few children by autoimmune-mediated neuropsychiatric abnormality, occurs in the paediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS). Population-based epidemiological studies not have been helpful in the identification of this association. The likely autoimmune basis of regressive autism suggests that any causal association with MMR vaccine would lead to a continuing upward trend in incidence after vaccine introduction - in developed-world but not developing-world populations, in parallel with other autoimmune diseases – rather than the reported epidemiological construct of a step-up-and-plateau model.

Recommendations

- That virological studies of children with ASD, including appropriately designed large scale epidemiology, are made a priority, and that the strategy for these investigations be set out by the working group, as described above.
- That immediate **active surveillance** of vaccine related adverse events be instituted, and that the responsibility for this surveillance be independent of those authorities either promoting vaccines, or involved in the manufacture or licensing of vaccines.

Conflicts of interest

I am the named inventor on a viral diagnostics patent in the area of Crohn's disease and ulcerative colitis. I derive no personal income or other finaincial benefits from this patent. Any future revenues from these patents will be used to fund our medical reserach programme into inflammatory diseases of the gastrointestinal tract.

I am acting as an medical expert in the current MMR class action in the UK

I hold no stock in any company and I am not in recipt of any grants from vaccine manufacturers.

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Congressman Dan Burton
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2157 Rayburn House Office Building
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17th May 2001

Dear Congressman Burton,

Thank you for your letter of May 7th 2001 and your kind comments. Further to the Hearing held by your Committee on 25th April 2001, I would like to commend you and your outstanding staff for your earnest desire to get to the bottom of the issues that surround the growing likelihood of a relationship between childhood vaccines and developmental disorders in children. In addition, I would like to follow-up on some significant issues raised at the hearing in relation to I) the testimony of Michael Gershorn ii) the implications of the IOM's report on MMR and autism and iii) the response to questions of Dr Berniers of the CDC.

i) Dr Gershorn's testimony

You will by now have received a letter from Professor John O'Leary in response to the wholly inappropriate and factually inaccurate testimony of Dr Gershorn that sought to discredit the molecular detection methodology used in Professor O'Leary's laboratory and, by extension, Professor O'Leary himself. Dr Gershorn's testimony relied upon information provided by Dr Michael Oldstone, with whom we had, until recently, a scientific collaboration funded by the University of California's MIND Institute.

As pointed out in Professor O'Leary's letter, you will observe that there were obvious errors made by Dr Oldstone in transcribing the data from the data sheets to the letter that was sent to Dr Amaral on February 15th 2001. Scientifically this is sloppy practice that should have been readily identified and rectified by careful review of the data. Under normal circumstances Dr Oldstone's errors would have been reconciled during the course of confidential scientific dialogue and he would

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have been spared any personal embarrassment. The opportunity for this has obviously been usurped by Dr Oldstone's inappropriate and untimely disclosure.

In addition, Dr Gershorn's testimony explicitly refers to tissues from uninfected control animals providing false-negative results. You will see from the data provided in Dr Oldstone's letter of 15th February and the data sheets provided from Professor O'Leary's laboratory, that this is factually incorrect. Tissues from uninfected animals are consistently negative in replicate tests.

To have forgone the due scientific process and to have provided these data to a third party (Dr Gershorn), and then to have them presented as a statement of fact, under oath, before the US Congress, defies belief. In view of the obvious errors, it would appear that Dr Gershorn also failed to check the source data before presenting them. This seems not only to reflect a lack of integrity on his part, but also has lead to what amounts to perjury before the US Congress, at the expense of the reputation of Professor O'Leary, a much valued and highly respected colleague. If Dr Oldstone were aware of the substance of Dr Gershorn's false testimony, then I would imagine that he too, may be considered to have perjured himself, albeit vicariously.

I have major concerns that these demonstrably false assertions have been disseminated widely within the vaccine and scientific communities. This could undoubtedly be used to prevent future publication and, thereby, impede progress in our understanding of the possible MMR-autism relationship. In addition, there are major implications for the reputations of the aggrieved scientists. The record must be set straight. I will not stand by and let shoddy science, unprofessional behaviour, malicious disinformation and lack of regard for the wider implications of this valuable work, compromise the standing of a much valued friend and colleague and the validity of the autism-vaccine debate.

In summary:

- Confidential data were transmitted to a third party, under oath, without permission of the collaborators;
- These data were disclosed by the third party in a public forum for the purpose of discrediting the techniques used to derive the data and the scientists utilising the techniques;
- The presented data were transcribed incorrectly by Dr Oldstone;
- The testimony of Dr Gershorn was false. It relied upon (1) inaccurately transcribed data and (2) the assertion that tissues from uninfected animals were positive for measles virus, when in fact they were consistently negative.
- The impression was given, by Drs Oldstone and Gershorn, that the techniques used by Professor O'Leary's laboratory falsely detected measles virus in uninfected cell cultures, used as a negative control. It is evident from the data that one of the RNA samples of apparently uninfected Vero cell sample that was sent for evaluation, was

contaminated with measles RNA. For the following reasons we believe that this occurred in Dr Oldstone's laboratory, and not in the laboratory of Professor O'Leary:

- TaqMan RT PCR is a sequence-specific reaction that will only yield a positive result if measles virus RNA is present in the submitted sample;
- All no-template controls for the TaqMan RT PCR, used during the analysis of the "contaminated" Vero cells, were negative. We are happy to supply all the raw data that confirm this;
- Solution-phase RT PCR and Southern blot analysis confirm both the contamination of the RNA sample and the negative status of the experimental controls;
- In the original analysis performed in Professor O'Leary's laboratory, the sample was contaminated with not one measles gene but two (F and HA) at virtually identical copy number ($1.5x10^2$ and $2x10^2$, respectively). This indicates contamination with measles virus or measles virus RNA. Since we use cloned copy RNA as controls for the respective F and HA-genes, and since the RT PCR reactions for these two genes are performed on separate occasions, the chances of dual contamination occurring on separate occasions and at the same copy number in Professor O'Leary's laboratory, are infinitesimally small to non-existent.
- Subsequent RNA extracted from uninfected Vero cells in Dr Oldstone's laboratory proved to be negative for measles virus. You will note from Dr Oldstone's letter of February 15th 2001, that where repeat samples were sent, they are designated either "Repeat test" or "Repeat test on same RNA". Dr Oldstone is very specific about the labelling of samples in this way. For the Vero cells, the repeat tests do not appear to have been performed on the same RNA, but presumably on RNA extracted from a second, truly uninfected and uncontaminated sample. Either Dr Oldstone was aware of a contamination problem with the original negative control sample from his laboratory, or there was insufficient RNA left over from this sample for RT PCR analysis, requiring him to prepare a second sample.
- Taken together, these facts provide substantial evidence that the source of the contamination was Dr Oldstone's laboratory.
- These issues could have been resolved by honest dialogue between collaborating scientists; they were not.
- In spite of the forgoing, the results have been used to damn the methodology of Professor O'Leary in a public forum, and thereby, all results deriving from his laboratory. The results actually suggest that is it is the scientific rigour and the data from Dr Oldstone's laboratory that deserve close scrutiny.

In light of these events may I prevail upon you, as Chairman of the Committee on Government Reform, to order an investigation into this issue. Professor O'Leary and I would be happy to co-operate, and Drs Oldstone and Gershorn must account for their actions and assertions, which may amount to defamation. If the irregularities that are identified above are borne out, it is difficult to see how either of these gentlemen can continue in their respective positions. Congressman Dr David Weldon has a very good understanding of the relevant issues, and may agree to helping with such an investigation.

ii) IOM Vaccine Safety Committee

May I turn now, to the issue of the IOM's meeting and report on the MMR autism debate. It is my understanding that this committee was convened at your request following the Hearing in April 2000. Also, I understand that it was your explicit request that the IOM committee should be comprised of members, free of conflict of interest. Accordingly, I attended at presented to that committee expressly on the understanding that the proceedings of this meeting would be heard and reported in a manner that was free from bias due to conflict of interest. In the light of certain revelations and the recent IOM report, I have several comments.

The IOM Committee's report was not free from conflict of interest. As you are aware, the report was sent out for review and recommendations-for-change, to senior members of the vaccine community (Drs Katz, Halsey and Miller) who have made public, in advance of the IOM meeting, their absolute opposition to the MMR-autism connection. This ill considered move by the IOM under the Chairmanship of Dr McCormick has, in effect, rendered the entire exercise devoid of credibility and a waste of time and effort.

The draft IOM report was also sent to some, but not all, of the presenters for the purpose of editing. Specifically, it was sent to Dr Eric Fombonne, an opponent of the MMR-autism connection, who presented novel, unpublished data to this meeting. The same courtesy and desire for scientific precision was not extended to me. This iniquitous handling of the IOM's affairs has turned the process into a farce, for which Dr McCormick must be held accountable.

iii) Response to questions of Dr Berniers

You may recall that during my testimony, I called for the immediate introduction of "Active Surveillance" for detection of possible adverse events to vaccines. The current system in the US and UK relies upon passive surveillance which, according to the FDA, identifies no greater than 1-10% of true adverse events. This is clearly unacceptable.

On the second day, Mr Waxman referred to my conclusion of the previous day, and asked of Dr Berniers – in a presumably prearranged question – whether there is a process of active surveillance in the US. He answered in the

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affirmative. He stated that all reported adverse events were actively investigated. The clear intention was to leave the Committee with the impression that there is a process of active surveillance in place in the US. There is not. I believe that Dr Berniers' statement in response to a contrived question was a deliberate attempt to mislead your Committee. I was alarmed at the way in which a Government official appeared to manipulate the Committee in a cynical attempt to obfuscate the issue of endorsing the greatest opportunity for monitoring vaccine safety in American children.

I urge the Committee to recommend to HHS for the immediate introduction of mandatory active surveillance for the detection of vaccine-related adverse events, on a nationwide basis. I believe that responsibility for this process should fall outside the jurisdiction, control or influence of those responsible for vaccine mandates, including the CDC, the AAP or anybody else with a conflict of interest in the vaccine policy-making process. The introduction of such a system would be a huge step forward in defining and ensuring the safest vaccine strategies for American children.

Once again, may I congratulate you and your staff on all your invaluable work.

Yours sincerely,

Andrew J Wakefield MB.BS., FRCS
Reader in Experimental Gastroenterology
Honorary Consultant in Experimental Gastroenterology to the Royal Free Hampstead NHS Trust
Director *Inflammatory Bowel Disease Study Group*

Cc Professor John J O'Leary
Representative Dave Weldon MD
Ms Liz Birt, Attorney
Mr Jim Moody, Attorney
Dr David Amaral, MIND Institute
Mr Rick Rollens MIND Institute

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Mr. BURTON. Thank you, Dr. Wakefield.

Do we have your entire report?

Dr. WAKEFIELD. Yes, Mr. Chairman.

Mr. BURTON. We will submitting these reports to the health agencies of this country and we will get a response from them after they review the reports.

Dr. Spitzer.

Dr. SPITZER. Thank you, Mr. Chairman.

I would like to ask with respect that if I need to be cutoff—because there has been a lot of work done since I was here at this committee last year—that I be allowed at least to share with you what is in the future, the research that has been planned, some of it that has been called for, and which is going to be undertaken by an intercontinental group in nine countries and three continents to deal with some of the issues because this is the first time it has become public—and appropriately so—because 1 year ago, here in this room, I decided to commit the rest of my epidemiologic career to exploring these issues, if nothing else, out of admiration for the families.

Mr. BURTON. We will allow you a little extra time. We have the other speakers. Because of time constraints, we have a little bit of a problem. But any additional information you have, you may rest assured will be put in the record and we will pass it on.

Dr. SPITZER. I will go as quickly as possible, particularly on those issues that are not specifically future-oriented.

The kind of research Dr. Wakefield does, with which I am familiar as much by the literature on an arms-length basis, is characteristic of laboratory and of clinical research which asks the question, can it happen? Epidemiology asks the question, does it happen? And then seeks answers in that direction.

The vast majority of the literature—and I have looked at pretty much everything the IOM looked at in the last 15 months on epidemiology—is inconclusive or uninterpretable answers. We are trying to remedy that, and I will explain why in questions or otherwise.

[Slide presentation.]

Dr. SPITZER. My perspectives are those of a professor of epidemiology and of public health medicine. I believe in immunization as the pillar of public health, but this does not mean that each new product can be exonerated from very careful evaluation, not just of effectiveness but of safety.

I have no sponsorship. The first time I have had coverage of my travel expenses was today. I work for no one. This is an initiative done without sponsorship and as neutral as I think can be attained normally. And I have no family members in the nuclear family or extended family with autism. That is not the motivation for my involvement, although that is a noble involvement.

Autism is an outcome—with very great respect for parents and families of children—that is as serious as death. It could not be less significant if I were involved in a mortality study resulting from MMR. The big differences are that the families of autistic children cannot grieve. It is their love, their commitment, and their undying optimism that masks the severity of autism. It is very important. It is part of the reason I made a commitment to the strategy for the future of autistic research.

The Institute of Medicine in a sense agreed. It said the disorders are incurable, permanent diseases that result in a serious developmental problem in children.

Incidentally, I was only able to get the executive summary. I came from overseas last night to be here. Where I was, I could not get the full report, so I can only quote the summary. If asked, I shall do that later.

I decided, having finished a review of much of the literature and the research literature on March 1st, approximately, when I submitted my paper to appear this month, that one has to really worry about autism based on the epidemiologic literature. And I will summarize it quickly. There is no evidence epidemiologically one way or the other that either rules in or rules out the problem.

A few days later, I was pleased to read the briefing document of Dr. Soto and his colleagues to the Institute of Medicine Committee, which reached pretty much the same conclusion—differences in words and emphasis—but pretty much the same. You cannot rule it in or rule it out.

Yesterday or the night before last, I saw that executive summary. You could interpret it the same way, but the wording and emphasis and what got to the press—the public relations version, if you wish—was that immunization is widely regarded as one of the world's most effective tools for protecting the public health and the evidence favors rejection.

If they are 48–52 percent, I am 52–48 percent. It is in the other direction. There has been no research that predicts the validity and interpretation of Dr. Wakefield's research, with which I have had nothing to do so far. Until that is set aside, I could not make that statement, although we are within percentage points, probably, of the verdict looking at the same literature.

There is a great deal found in the report that alludes to causation. In biological population science, you have to demonstrate association before you get to causation. Normally, unless the results are very dramatic, you have to invoke the laboratory and the clinical science at the same time as the population science to reach those kinds of conclusions following criteria such as the Bradford Hill criteria, much as the surgeon general did with smoking of cigarettes 30 years ago or so.

So we have not gotten to association yet. None of the studies have gotten there, and certainly—say, the Taylor Study—cannot refute or confirm association, certainly not causation. That study mandated in the United Kingdom just does not prove anything. It is a preparatory, preliminary, hypothesis-generating study, not a hypothesis-testing study. And that is where we need to go.

These are the headings—I will go over them very quickly, Mr. Chairman—the issue of the epidemic of autism, natural history of autism—I will let you read them for a minute.

Speaking as an epidemiologist, there is an epidemic. It is not refutable on the evidence that is there. I am saying it, even though the great majority—except for one or two studies—they are all prevalence studies. A prevalence study is inexpensive and that is why one leans in that direction with the meek resources that are given for this kind of research. You need incidence to clearly demonstrate or refute an epidemic.

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And the one peer-reviewed published study that did incidence—which is a case study out of the Boston Collaborative Surveillance Unit at Boston University, based on the British data base—it is an incidence study and it shows an epidemic. It is a seven-fold increase.

In California, you reported yourself, Mr. Chairman, that there are 700 new cases—which is incidence—in the past 3 months. Compared to the same seasonally adjusted period of 3 months 7 years ago, that is a 404 percent increase. That is an epidemic.

In Ireland, just the day before yesterday, there is a three-fold increase in prevalence done in the last few months. And in Cambridge University, a study showed a 10-fold increase in prevalence. These are numbers that are not the basis upon which you question an epidemic. We have an epidemic of autism and I assert that, as an epidemiologist, with confidence.

There is a widespread assumption that the autistic symptoms typically do not emerge until the child's second year, about the same time that MMR is first administered, a sensible observation made in the executive summary of the IOM. And you, Mr. Chairman, in your introductory comments asked for the science about all this.

I have been working pro bono with the autistic families in the United Kingdom, who are challenging Merck, Smith-Kline, and others about the possible association. In documents I read of the attorneys of those companies, the statement was that 55 cases of autism were reported worldwide in the last 20 years of children with autism.

But I said, wait a minute. There are 505 cases in this list here. Where do they get that? Apparently, they are reported on the wrong color of paper to the yellow card system, so it does not make it into the official statistics.

So I decided that we should do an observational exercise—I barely call it a study—abstracting each of the medical records of these children and having some summaries to help us understand what is going on. We did it. I had an interdisciplinary team do this natural history of autism on a self-selected sample. I admit that. This is not representative of anything. We did not even do statistical tests for that reason.

The children had to be less than 15. They had to be free of symptoms not only before MMR but for the first 30 days after to bias it against us. All symptoms, signs, and diagnosis had to be in writing by a health professional, not just casual reporting—which is meaningful, but nevertheless difficult to validate.

We ended up with 493 medical records that could be used. I was sort of sobered. I entered a room that was full floor to ceiling and wall to wall with records. There was not enough space to work, but we did it anyhow. The average width of a chart was three volumes totaling more than 10 inches. That is what we were looking at.

This was looked at independently by the professor of family medicine of McGill, by a clinical psychologist from the University of Glasgow, by myself as an epidemiologist, and we had research assistants helping us with the tasks. It was a descriptive analyses only, as I said. I am reporting it for the first time. We met last Friday for the final analysis. We may end up by one-half percent because I questioned three records, which are being checked on now. That is what we were doing last Friday and we are writing the paper now, which should be sent in a week or so.

So there you see 493 medical records. The numbers there for exclusion, the 372 eligible subjects—most of the ineligibility was that they had symptoms early on and we wanted to bias it against us. We had 70 percent of those cases as classic autism; 7 percent were atypical autism; aspergoes were 8 percent. Of those cases, 40 percent were regressive, 40 percent were failure to develop, and 9 percent were both.

But most importantly—and that is with reference to the evidence you were looking for—this is not good scientific evidence, but it is a start—if you see there, the median years from receiving the first dose to making the diagnosis was 2.6 years. That means that half the cases were 2.6 and greater. And there was great variation.

If you look at average, which is a bit higher, it is 3.2. But the median is more accurate because of the distribution. And the range is from 0.5 to 11.9 years of delay. The correlation does not even exist, the date of vaccination and the onset of this category of diseases.

I would just like to allude to this, Mr. Chairman. I have been looking for 17 months for studies with scientific admissibility that are adequate pharmacological-epidemiologic evidence of safety, which you would need when a concern has arisen in the community about safety of a particular drug. I have not found any. I have not found it. A proper study of safety under the current conditions, given the frequency of the disorder, would require about 450,000 children. I went through that with statisticians at Cambridge. And that has never been done.

And the "safety studies" published are of scores of patients. That is a type of sample size which is simply inappropriate, insufficient, and not a scientific way to look at the safety of a drug. I am astonished that the authorities in the United Kingdom, the United States, and my country of Canada are not requiring it the same way they have required us to do it for all contraceptives, for the right reasons.

The problem is incorrect length of followup as much as anything in these cases. For instance, the Medical Research Council report widely cited in the United Kingdom as setting aside the concern followed an unrepresentative subsample of the sample of children I looked at for 3 to 6 weeks when the range is from 0.5 years to 11.8 years. The study is simply not valid for that reason alone and cannot be invoked to demonstrate safety or the lack of a need for concern.

There is no problem if you do not look. The companies know that. Those of an opinion that there is no association say that epidemiologists have shown no evidence. Of course, they have. And they have all been small studies. I call them phyto studies to my students. Phyto means arenal products in the ocean. It doesn't make any difference in the levels in your understanding.

Nobody has looked. And the cost of looking is that of millions of dollars. Is that OK? Yes, it is OK. Look at the millions of dollars of profits. One way of pretending you are looking but not looking is by under-powering the studies. They are not powered sufficiently high to be able to deal with the no-difference issue leading you potentially to what we call a type two error statistically.

I will just tell you—and it is in the written record—the Finnish study reported widely by the press in Britain—much like likely the IOM reports will be somewhat misrepresented—does not in any way demonstrate safety or lack of it because it is a passive surveillance study designed for other purposes and then reanalyzed for another reason. I give a page and a half of reasons why that study just does not mean anything one way or the other. It is in the written record, Mr. Chairman.

Research priorities—I will list them quickly and I will end up with the study.

Ongoing research in laboratory and the clinic—I will not say any more. A lot has been said about treatment, but I would add a word that I hardly ever hear and that is about palliation. The families need treatment as much as the children, and palliative strategies need to be undertaken. I am sure my clinical colleagues couldn't agree more with that. But it does not get priority in potential focus of support.

Correctly designed safety studies. Correctly designed incidence studies. And case-controlled studies.

This past Saturday and Sunday, we met at Heathrow Airport, representatives from six countries out of nine possible candidates, to decide go/no-go on a major intercontinental study. The IOM said the committee does propose targeted research efforts and more rigorous data-gathering procedures. Much of the problem in existing research is that you are going into data that were created for a purpose other than exploring that hypothesis. That is a lot of the problem. This is going to get around that.

Mr. BURTON. Doctor, are you about to wrap up?

Dr. SPITZER. I need 3 more minutes, or less, if I can.

We reached a "go" decision on Sunday, a few days ago. We have been working on it since. I am going back to it.

We are going to explore risk factors other than MMR as well because there is no point going in 5 years and then deciding that we should have looked at something else. We are going to try to avoid that.

The candidate countries are on the slide, nine countries. Why so many countries?

In England, Canada, Denmark, and the United States there is such an overwhelming coverage that obtaining control is almost impossible. You have to have control. The contestants of clinical science and epidemiology and laboratory science as well is comparison. Without comparison, you have generation of hypothesis in the main, very seldom testing of a hypothesis.

You ask in epidemiology, how is your spouse? And you will probably hear something like, compared to whom? [Laughter.]

You have to have comparison, and that is why we are proposing a case-controlled study, and to do much of it in-country. Poland only has 35 percent coverage today. The rest is univalent. The same with Argentina and the same with France.

Selected features of the study—quickly—3,500 cases and 7,000 unaffected controls. Exposure risk factors: MMR, mercury, other vaccination, childhood diseases, genetic factors, not to be exhaustive but as examples. The outcome is the entire spectrum of autistic disorders.

Why 3,500 cases? Because, as has been said by many already—and I am pleasantly surprised—we will likely find the problem in a subset. It is a multifactorial problem, almost certainly everyone seems to agree. But we do not know what that subset is in advance.

I would propose that a subset of less than 10 percent—it is either not discoverable or not as important. So we are making 10 percent the threshold. That gives you 350 cases and the corresponding control that may give us important answers.

Finally, it is investigator-initiated. We are not responding to any request for proposal, therefore we have to create the protocol and then "sell it" to objective, independent organizations. The cost is estimated to be $17 million to $21 million over 5 years, $125,000 in the first year.

Is that a lot? It is the equivalent to the annual cost of care and support of 0.3 percent of autistic children in the United States alone. We have only methodological support from the United States so far. We have support from most of the other countries. We will do it. We would like to work with the United States. We do not need the United States or the United Kingdom, for that matter. We hope we can push ahead with this and look for some of the answers that are being called for.

I apologize for the delay. Thank you for your attention.

Mr. BURTON. Thank you, Dr. Spitzer. We will take your whole program and submit that, along with the others, to HHS and ask them to take a hard look at that.

Dr. Haley.

Dr. HALEY. I am probably one of the few people here who does not treat patients. I am a research scientist and I work in a lab.

I was asked some time ago to look and go to the bottom line. Are the vaccine mixtures that we are placing in the children toxic? If they are going to have an effect on autism or any disease or any neurological disorder, there is a good possibility, if it comes from the chemical level, that vaccines have to show some toxicity at the molecular level.

We did test vaccines, and I will make this very short because I know we are in a hurry.

We compared the vaccines with and without thimerosal from the same source, the same type of vaccine, and those with thimerosal present were remarkably much more toxic—over 10-fold to 100-fold more toxic than those without thimerosal. There was one outstanding exception, and that was the MMR vaccine. The MMR vaccine was as toxic as the vaccines with thimerosal, but there is no thimerosal in the MMR. We measured mercury levels, and I think the thimerosal is not there, but we would want to do a lot more numbers of vaccines.

But there is something in the MMR vaccine that does inhibit the enzymes and the brain protein systems that we have very dramatically. I do not know what it is.

I would point out also that the toxicity is thimerosal in a vaccine mixture. In our studies, we looked at combined toxicities because, we are not rats living in a pristine cage. Aluminum is a neurotoxin, formaldehyde is neurotoxic, and you throw that in with thimerosal, which breaks down to ethyl mercury, a well-known toxin. You do not know what you will get without doing studies. I have looked hard and cannot find them. I am surprised they were not done, but not totally. This is just something we do not know the answer to.

We do know that ethyl mercury is very, very toxic. Of the studies you can read about, of the three children that have been intoxicated that I have found—they all died with 1 microgram per ml levels. That is considerably below what they would do, but you just do not hit a point and then die. You start a linear progression of health effects.

The other thing, when we talk about the level of mercury that is toxic, you cannot compare mercury to ethyl mercury to dimethyl mercury. They are different compounds. Ethyl mercury, methyl mercury, and especially dimethyl mercury are much more toxic than an equivalent amount of mercury on the atom or mole basis. So you cannot compare them.

I would also point out that the reason mercury does not kill us immediately is that a lot of it depends on our health. We all live at a level where we have reducing equivalents this high when we are 20 years old. We are full of spit and vinegar. And the mercury level is down here and we are handling it real well. As we age, the level of glutathione, metallothione, and other proteins that we synthesize in our bodies—because the energy level drops down—gets to the point where we are getting more balanced. When we get too old or too unhealthy, then we pass this. Then the mercury can take over and start having the effect of damaging the healthy proteins, the proteins we really need in the body.

I would also point out that this level can drop precipitously if you have a viral, bacterial, or fungal infection. It will drop dramatically because it is fighting to take care of the oxidants because the molecule that removes mercury from our body is also the molecule that takes care of the reactive oxygen species, the normal aging products, and the materials we call oxidating stress products.

I am surprised, when I understand the data that they are presenting here—we know certain children are born that are autistic. These vaccines need to be cleaned up because even if they did not cause it, who would want to give ethyl mercury to a child that is destined to get autism? It is a very poor idea. You really need to clean the vaccines up. I cannot imagine why they did not take the vaccine mixture and test it, on the very base level in a test tube against a bank of enzymes or against a brain homogenate to see whether or not they were injecting toxicants into these children. It is very clear that has happened.

I would also point out that we have a problem with combined toxicities. People that smoke are heavy in cadmium. And cadmium and mercury, if you combine them together in a test tube and test system against tubulin—which is probably the first protein affected in Alzheimer's Disease—that you can have a non-toxic level of mercury, a non-toxic level of cadmium, and you add those two together and you will get over 50 to 60 percent toxicity on a comparative basis.

Combined toxicities and the multiplicity of the events that are caused by mercury—mercury is somewhat similar to alcohol in that when different people get exposed to it they behave differently—so it is very difficult when you want to look just at someone who is an autistic. To me, that is a name and it is a tantology. Autistics do this. And yet, I say, do all autistics do that? No. Then there is a difference. They are not the same. You have to look at them differently. So we have a very confused issue here that I think we need to look at.

I would also point out that in the vaccine issued, the one thing that really makes the vaccines toxic to infants—you are giving the same shot to an infant that you give to a 180-pound soldier. Infants do not have bilary transport. They do not make bile when they are first born and for some time after that. The bilary transport system is how the body removes mercury from the system. Babies cannot do that. So it is the equivalent of drinking alcohol and not being able to metabolize it. It builds up. It would stay there and be much more damaging to an infant than to someone who is an adult who had the ability to rid the body of the mercury.

Aluminum is removed by the renal system. Infants have an immature renal system. They cannot handle heavy metals and get rid of them as fast as we can. If you give them multiple shots with high levels of mercury, I do not know how well they handle it. I have not been able to find any data where this has been tested. So the mercury and aluminum levels would buildup in these infants if they had multiple shots before they got to the point where their bilary and renal systems were totally mature.

The aspect of genetic factors—I was in New Zealand I talked to a doctor by the name of Mike Godfrey. He is a friend of mine and he and I have talked a lot about Alzheimer's Disease and the involvement of mercury. Johns Hopkins University showed several years ago that there is a risk factor, a gene called APO-E protein. There are three copies, two, three, and four. Two is protective against Alzheimer's Disease; four puts you at high risk for the disease.

If you look at the chemistry of the APO-E proteins, this can be reflected in the fact that it is a housekeeping protein that clears the brain of waste materials. If you have APO-E2, you can carry out two atoms of mercury for every atom of APO-E that goes out. If you have APO-E4, you can carry out none.

He took this and looked at autistic children. When he did the screen of autistic children, there was a huge preponderance of them that had APO-E4, indicating that there is a genetic risk factor which deserves further study. And it does implicate that the inability to detoxify the cerebral spinal fluid may be at least part of the neurological aspect of this disease. I am not a physician, so I do not go there to make answers about that.

I have also been in a fight with the pro-dental amalgam people for many years, as I did research about 10 years showing that mercury dramatically inhibited the same enzymes that are dramatically inhibited in an AD brain. And everyone says there is not enough mercury there to do it. Recently—and it is in the report I did—they have found that studies using neurons and culture, that levels of mercury approximately 100 to 1,000-fold less than you have in your brain, when you place it with neurons in culture will cause the formation of the two diagnostic hallmarks of Alzheimer's Disease.

I went to NIH and screened the grants they fund. We found one where they are funding the ability to make a better amalgam that would leave less mercury because there was some concern about the mercury being released, which, according to the ADA is a totally safe level. But there are no grants looking at the effects of low-level mercury exposures to Americans. But we are placing grams in our mouth and micro grams in our vaccinations.

I cannot say, nor would I say, that vaccinations cause autism. However, if the data holds up that I have been seeing with the relationship, I think it is an awfully good suspect, at least one of the co-factors that might aid in the onset of this disease. So I would really recommend and encourage you to put some pressure on NIH to look at the contribution of different forms of mercury we put in our medicines and in our dentistry to see what effect they have on the neurological health of Americans, especially autistics.

Thank you.

[The prepared statement of Dr. Haley follows:]

TESTIMONY OF BOYD E. HALEY, PROFESSOR AND CHAIR, DEPARTMENT OF CHEMISTRY, UNIVERSITY OF KENTUCKY

Government Reform Committee, Dan Burton (R-IN), Chairman, 25 April 2001

Recently, I was requested to do an evaluation of the potential toxicity of vaccines containing thimerosal as a "preservative" versus those vaccines not containing thimerosal. The results were very dramatic as shown in the accompanying Table attached to this document. In our preliminary studies, vaccines containing thimerosal as a preservative, consistently demonstrated *in vitro* toxicity that was dramatically greater than the non-thimerosal or low thimerosal containing vaccines. This data was obtained by comparing the toxicity of the vaccines with solutions of pure thimerosal and with solutions of mercury chloride. The biological testing material was both (i) brain homogenates and (ii) a mixture of four purified mammalian enzymes. The data was not unexpected as thimerosal and other compounds containing a similar thiol-organic mercury group are widely known to be especially potent neurotoxic agents. Our results are very consistent with the reported toxicity of thimerosal containing vaccines versus non-thimerosal containing vaccines as observed in cell culture studies reported in 1986. The chemical rationale for the neurotoxicity of thimerosal is that this compound would release ethyl-mercury as one of its breakdown products. Ethyl-mercury is a well-known neurotoxin. Further, combining thimerosal with millimolar levels of aluminum cation plus significant levels of formaldehyde, also found in these vaccines, would make the vaccine mixture of even greater risk as a neurotoxic mixture. Using this vaccine mixture on infants who do not have fully developed bilary (liver) and renal (kidney) systems could dramatically increase the toxic effects, especially if they are spuriously ill. The toxic effects of exposure to thimerosal in infants cannot be reasonably compared to those observed in adults made toxic by exposure to similar ethyl-mercury containing compounds. Mercury is primarily removed through the bilary system and aluminum is removed by the renal system. Inability to rid the body of these toxicants would greatly increase the damage they are capable of doing in infants. Additionally, I can understand the necessity of using an anti-microbial "preservative" in vaccines to prevent contamination. I cannot understand the prior and continued use a "preservative" that breaks down into a well-known neurotoxin. While I do not have the data to unequivocally state that exposure of infants to thimerosal is causal for autism, it seems to be the best suspect if the data on the relationship to vaccinations and autism hold true.

Since about 1989 my laboratory has been actively involved in research regarding the toxic effects of elemental mercury and the relationship of this toxicity to neurological diseases, primarily Alzheimer's disease. One fact that has become extremely obvious to me during this past 11 years is that it is impossible to determine the exact toxic level of mercury or mercury containing compounds that is safe for all individual humans. There are several reasons why organic-mercury, and elemental mercury, should not be considered safe for humans at the measurable levels currently reported as "safe" by current monitoring agencies which I will detail below.

First, each human would likely have a level of toxicity from other mercury and non-mercury containing sources. These environmental toxicants could work synergistically with ethyl-mercury rendering the ethyly-mercury much more toxic than it would be in the absence of these other toxicants (e.g., elemental mercury from dental amalgams, cadmium from smoking, lead from paint and drinking water, aluminum, etc.). Humans are not rats in a pristine cage, eating rat chow carefully prepared to eliminate any toxicants. Humans smoke, drink alcohol, have numerous mercury emitting amalgam fillings, eat questionable food, and drink water known to contain other toxicants. In my laboratory we have tested the combination of elemental mercury with some of the other toxicants and the data, not unexpectedly, shows a great increase in toxicity of equally added amounts of mercury. Therefore, an infant with prior mercury or other heavy metal exposure would likely respond more acutely to the thimerosal in vaccines.

Second, the detrimental effect of any specific level of mercury would have on any one individual's metabolic system would be directly proportional to the (A) the level of "protective bio-compounds" (e.g., glutathione, metallothioine) that exist within that person on the time of exposure and (B) the ability to physiologically clear such toxicants from the body. The level of the protective compounds would certainly be directly dependent on two factors, age and health. Infants, with their immature physiology and metabolism would not be expected to handle mercury as efficiently as mature adults. The elderly have been shown to have decreased "protective" glutathione levels compared to middle aged and young adults. The aged are also more susceptible to oxidative toxicants such as mercury. Consider also that infants do not make bile in their early months of life and are unable to remove mercury through bilary transport, the

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major route for mercury removal. They also do not have a fully developed renal system that would remove other heavy metals as effectively as adults. The elderly also have weakened immune systems and are more susceptible to microbial infections. Such infections are known to lower the biochemical energy level and, further, to reduce the neurons ability to synthesize the protective proteins that bind and remove heavy metals. The age factor must always be considered for response to heavy metal exposure as well as spurious microbial infections.

Third, genetically susceptibility is of critical importance. For example, other researchers have shown that genetic carriers of the brain protein APO-E2 are much less susceptible to Alzheimer's disease (AD) whereas genetic carriers of the APO-E4 genotype are at enhanced risk for developing AD. APO-E proteins are synthesized in the brain with the assigned physiological task of carrying waste material from the brain to the cerebrospinal fluid, across the blood-brain barrier into the plasma where the material is cleared by the liver. The biochemical difference between APO-E2 and APO-E4 is that APO-E2 has two additional thiol groups, capable of binding and removing mercury (and ethyl-mercury) that APO-E4 does not have. The second highest concentration of APO-E proteins is in the cerebrospinal fluid. Therefore, it is my opinion that the protective effects of APO-E2 is due to its ability to protect the brain from exposure to oxidants like mercury and ethyl-mercury by binding these toxicants in the cerebrospinal fluid and keeping them from entering the brain. Recent data presented by Dr. Mike Godfrey of New Zealand indicates a similar APO-E risk factor exists for autism and this needs to be investigated further. However, I do strongly object to labeling those "genetically susceptible" individuals as "having a genetic disease" because they are the first injured on exposure to modern toxicants. Humans did not evolve breathing mercury vapor or having organic-mercury compounds injected in them as infants.

Fourth, the inability to see the effects of chronic, low level toxicity on human health is most likely our greatest failing as intelligent beings. For example, within the past year two publications in refereed scientific journals have emerged from major foreign research universities demonstrating that mercury can induce the formation of the two major pathological diagnostic hallmarks of Alzheimer's disease. This occurred at concentrations near or below the levels of mercury found in most human brains tested. First, mercury has been shown to induce an increase in amyloid protein secretion (the component of amyloid plaques) and to increase the phosphorylation of a protein called Tau *{see Oliveri et al., J. of Neurochemistry,V 74, p231, 2000}*, and to produce neurofibillary tangles *{Leong et al., NeuroReports V12(4), 733, 2001}*. All of this was done with neurons in culture and represent observations found and considered diagnostic of Alzheimer's disease. This work is in agreement with data published earlier from my laboratory in refereed articles and summarized in one single article *{Pendergrass and Haley, Metal Ions in Biological Systems V34, Cahpter 16, Mercury and Its Effects on Environment and Biology, Siegel and Sigel EDS., Marcel Dekker, Inc. 1996}*. This data basically demonstrated that addition of very low amounts of mercury to normal human brain homogenates inhibited two critical enzymes that were also dramatically inhibited in Alzheimer's diseased brain. The straight-forward conclusion is that any exposure to mercury vapor would exacerbate the medical condition classified as Alzheimer's disease and one would even have to consider low level chronic exposure to mercury as a contributor to the etiology for this disease. Yet, we are continually told that levels of mercury from dental amalgams could not do any harm and that it is just totally appropriate to add this exposure to our already significant exposure to toxicants.

The rationale why all, or most of us do not have AD since we mostly do have significant mercury levels in our tissues is most likely as follows. We all have a certain level of "protective proteins (e.g. glutathione)" in our brains that bind to and render mercury much less toxic and aid in the removal of the mercury from the body. Once this protection is overwhelmed our neurons are likely in jeopardy. Many factors are involved in reduction of glutathione and other protective proteins against heavy metal toxicity. The most obvious are age, disease and APO-E genetic susceptibility. As we age we are much more susceptible to disease and the overall cause of this is a weakened immune system and a less effective metabolism. Therefore, while getting amalgam restorations at 20 years of age may not show much immediate effect on the healthy we have to consider what happens as humans approach 60 to 70 years of age, especially the genetically susceptible.

It is very difficult to prove that mercury or organic-mercury compounds cause any specific disease that is identified by its related symptoms. This is mostly due to the high numbers of confounding factors presented in the current human environment. Also, the multiplicity of biochemical, physiological and clinical responses by different patients to the same mercury based toxicants adds to this confusion. However, since infants get autism and related disorders, and many of our aged are afflicted with AD, Parkinson's, etc., we know that they have crossed the thin-red line into the neurologically diseased state.

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There can be no doubt that the purposeful use of mercury in medicine and dentistry, especially if it was prolonged and excessive, would significantly contribute to the onset of their disease. I congratulate those who effected the removal of thimerosal from children's vaccine. Now I encourage all involved to remove thimerosal from all vaccines and especially those that our elderly are encouraged to take for flu and allergies.

Finally, academic medicine has searched long and hard without success to identify vectors that cause many of the neurological diseases such as AD, ALS, MS, Parkinson's, etc. The NIH has spent huge amounts of funds on the study of amyloid protein, tau protein and neuro-fibillary tangles in the unsuccessful search for the cause of AD---now it has been demonstrated that mercury at very low concentrations can cause neurons in culture to form these protein abnormalities that are the diagnostic hallmarks of AD. Exposure of brain tissue to mercury also specifically inhibits other enzymes/proteins known to be inhibited in AD brain. Yet, there has been a paucity of NIH funds spent to study the potential neuro-toxicity of mercury routinely placed in human contact by medicine and dentistry. I would like to encourage the members of this committee to support extended research into the potential causal and/or exacerbation relationship of mercury to these neurological diseases and to support studies to improve the therapeutic treatment of autism and related disorders.

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EFFECT OF VACCINES ON ENZYME ACTIVITY

Vaccine:	I	II	III	IV	V	VI	VII
0	100%	100%	100%	100%	100%	100%	100%
1.25	10.4%	100%	18.7%	100%	4.4%	62.5%	15.1%
10	0%	23.7%	0%	79.9%	0%	26.8%	0%
Presev.:	Yes	No	Yes	No	Yes	No	No

I: DIPHTHERIA/TETANUS (TRIPEDIA) WITH PRESERVATIVE
II: HEPATITIS B (ENERGIX-B) NO PRESERVATIVE
III: HEPATITIS-B (RECOMBIVAX-HB) WITH PRESERVATIVE
IV HEPATITIS-B (RECOMBIVAX-HB) NO PRESERVATIVE
V: HAEMOPHILLIS B (WITH PRESERVATIVE)
VI: HAEMOPHILLIS B (NO PRESERVATIVE)
VII: M M.R. (NO PRESERVATIVE)

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30 May 2001

The Honorable Dan Burton
Chairman
Committee on Government Reform
U.S. House of Representatives
Washington, D.C.

RE: May 11th letter by Robert M. Anderton, D.D.S., J.D., LL.M. and President of the ADA, challenging my statement to the Committee on Government Reform looking at the topic, Autism-Why the Increased Rates? A One Year Update.

Dear Mr. Chairman:

At the April 25th meeting of your committee I gave testimony that the President of the American Dental Association (ADA) takes exception to in a letter sent to you dated 11 May 2001. Quoting from that letter the testimony the ADA dislikes is *"that elementary mercury from dental amalgam could work synergistically with other ethy-mercury sources and have a cumulative toxic effect on the body. Dr. Haley postulated that this could be a potential cause of autism and Alzheimer's disease."* I stand by my statement as a sensible concern based on published scientific research regarding synergist toxicities caused by two very toxic agents, mercury and the organic mercury compound thimerosal. This concern is elevated since mercury exposure from amalgams to a pregnant mother concentrates in the fetus and a single vaccine given to a six-pound newborn is the equivalent of giving a 180-pound adult 30 vaccinations on the same day. Include in this the toxic effects of high levels of aluminum and formaldehyde contained in some vaccines, and the synergist toxicity could be increased to unknown levels. Further, it is very well known that infants do not produce significant levels of bile or have adult renal capacity for several months after birth. Bilary transport is the major biochemical route by which mercury is removed from the body, and infants cannot do this very well. They also do not possess the renal (kidney) capacity to remove aluminum. Additionally, mercury is a well-known inhibitor of kidney function. Common sense indicates that the concern I expressed should be taken seriously since we do not know how combined toxicities effect humans, especially *in utero*. Consider the current epidemic death on birth of over 500 foals from apparently healthy mares around Lexington, KY. These deaths were identified as being due to a low level toxicity delivered by caterpillars eating poison plants and later, on migration, depositing their waste products on grass being eaten by the mares. The point being it is the infant *in utero* that suffered most on exposure to low level, toxins, not the mpther. Combined mercury toxicities can be devastating as I reference below and in the many references available on the www.altcorp.com website. What is needed is research by non-biased scientists to clarify this, something our FDA and NIDCR have refused to do. As the American public

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find out what has happened regarding this issue, they will be quite angry. This is a biomedical science issue that should have been resolved a long time ago by the responsible federal agencies.

Below I present detailed and referenced information supporting my case and respond to various statements made by the ADA President that I believe to be misleading and sometimes flagrantly wrong. The ADA seems to think it has the right to select which research it believes and to trash that research that says it is wrong, even though the latter represents the bulk of published research. To address the issues raised by the ADA President in his letter I will go in sequential order of the comments made in the letter placing the ADA comments in italics and providing scientific references for my conclusions.

"There is no scientifically valid evidence linking either autism or Alzheimer's disease with dental amalgam". First, mercury is a well-known, potent neurotoxicant, and common sense would lead to the conclusion that severe neurotoxins would exacerbate all neurological disorders, including Parkinson's, ALS, MS, autism and AD. Several research papers in refereed, high quality journals and scientific publications have shown that mercury inhibits the same enzymes in normal brain tissues as are inhibited in AD brain samples (1a-c, 2, 3). AD is pathologically confirmed post-mortem by the appearance of neuro-fibillary tangles (NFTs) and amyloid plaques in brain tissue. Published research, within the past year, has shown that exposure of neurons in culture to sub-lethal doses of mercury (much less than is observed in human brain tissue) causes the formation of NFTs (4), the increased secretion of amyloid protein and the hyper-phosphorylation of a protein called Tau (5). All three of these mercury-induced aberrancies are regularly identified as the major diagnostic markers for AD. In the manuscript published in the J. of Neurochemistry (5) the authors state "These results indicate that mercury may play a role in the patho-physiological mechanisms of AD." In most of these experiments, mercury and only mercury among the several toxic heavy metals tested, caused the AD related responses reported. Many medically trained individuals would agree that if something causes the appearance of the pathological hallmarks confirming the disease then it likely causes the disease. I at least have limited my claims to exacerbation of these diseases to err on the side of caution.

Further, consider this about AD. A study of 500 sets of identical twins from World War II era lead to the conclusion that sporadic AD which represents 90% of the cases was not a directly inherited disease. In many cases one twin would get AD and the other would not. Genetic susceptibility is involved, but a toxic exposure is required (e.g., if you are genetically susceptible to being an alcoholic you still need to be exposed to alcohol to become one). The work by Rose's group at Johns Hopkins University implicates APO-E genotype as a "risk" factor with APO-E2 being protective and APO-E4 being a major risk factor. APO-E2 has the ability to protect the brain from mercury by having two additional thiol-groups to bind mercury appearing in the cerebrospinal fluid whereas APO-E4 does not have this additional capability (1). This may explain the proven genetic susceptibility to AD of the APO-E4 carriers.

NIH has spent hundreds of millions of dollars to find a causal factor for AD. Yet, no virus, yeast or bacteria has been identified so the cause remains unknown to general science. The rate of AD per 1,000 population is nearly the same in California, Michigan, Maine, North Carolina, Florida, Texas, etc. It is not significantly different for rural versus urban individuals, or factory workers versus those with outside jobs. So the primary toxicant that may be involved is most likely not environmental. Therefore, it must be a very personal toxicant, like what you put in your mouth. Since we place grams of a neurotoxic metal, mercury, in our mouths in the form of dental amalgam this makes it a good suspect for the exacerbation of AD---not that all would be affected, just those that are genetically susceptible, or those who become ill enough to fall prey to the toxicity, or those that are also exposed to another synergistic toxin (see below).

The one fact that ties mercury into a major suspect for AD is the fact that most of the proteins/enzymes that are inhibited in AD brain are thiol-sensitive enzymes. Mercury is one of the most potent chemical inhibitors of thiol-sensitive enzymes and mercury vapor easily penetrates into the central nervous system (2). Mercury is not the only toxicant to inhibit thiol-sensitive enzymes. Thimerosal and lead will do this also as well as reactive oxygen compounds created in oxidative stress and many other industrial compounds. However, mercury has been reported to be significantly elevated in AD brain (14a,b, 15). Mercury is in many mouths being emitted from dental amalgam and absolutely would exacerbate the clinical condition identified as AD. Therefore, mercury should be considered as a causal contributor since mercury can produce the two pathological hallmarks of the disease and inhibits the same thiol-sensitive enzymes that are dramatically inhibited in AD brain.

It documented by a 1991 World Health Organization report that dental amalgams constitute the major human exposure to mercury. Grams of mercury are in the mouths of individuals with several amalgam fillings. Further, the level of blood and urine mercury positively correlates with the number of amalgam fillings. This was confirmed by a recently published NIH funded study (6). Therefore, I fail to see the ADA's viewpoint that there is no scientifically valid evidence linking mercury from amalgams to exacerbating AD, especially since mercury produces the diagnostic hallmarks of AD (4,5). The ADA hides behind the fact that there has not been an epidemiological study to attempt to correlate mercury exposure and AD. However, absence of proof is not proof of absence. This also begs the question why the ADA, the FDA and the National Institutes of Dental Craniofacial Research (NIDCR) have not pushed for such a study? These agencies know this would be immensely expensive and only the U.S. government could afford to support any reliable long-term study. Yet, these same responsible agencies have failed to confirm as safe the placing into the mouth of Americans grams of the most toxic heavy metal Americans are exposed to. The dental branch of the FDA has steadfastly refused to investigate the toxic potential of dental amalgam.

Look at the references in the ADA letter! Even they must quote Scandinavian literature to support their contentions of safety, and even then they have to reference papers on fertility instead of neurotoxicity! Where is the ADA, FDA and NIDCR supported U.S. research in this area? Go to the NIH web-sites and look for research on the safety of mercury from amalgams, or try to find an NIH study concerning possible mercury involvement in any common neurological diseases. NIH does support research on methyl-mercury, as we seem to like beating up on the fishing industry whilst leaving the dental industry alone. However, according to the NIH study about 90% of the mercury in our bodies is elemental mercury, not methyl-mercury, showing the exposure is more likely from dental amalgams rather than fish (6). Support at NIH has been very sparse for investigating the relationship of elemental mercury exposure to neurological diseases.

"And there is no scientifically valid evidence demonstrating in vivo transformation of inorganic mercury into organo mercury species in individuals occupationally exposed to amalgam mercury vapor". There was a paper published entitled "Methylation of Mercury from Dental Amalgam and Mercuric Chloride by Oral Streptococci in vitro" (19). This strongly indicates that "organo mercury species" are indeed capable of being made in the human body and may explain the appearance of methyl-mercury in the blood and urine of individuals who don't eat seafood.

Further, periodontal disease is considered one of the major risk factors for stroke, heart and cardiovascular disease and late onset, insulin independent diabetes. Many studies of the toxicants produced in periodontal disease have identified hydrogen sulfide (H_2S) and methane-thiol (CH_3SH) as major toxic products of infective anerobic bacteria in the mouth metabolizing the amino acids cysteine and methionine, respectively. These volatile thiol-compounds are what cause bad-breath! Methane-thiol (CH_3SH) would react immediately and spontaneously in the mouth with amalgam generated mercury cation to produce the following two compounds, $CH_3S\text{-}HgCl$ and $CH_3S\text{-}Hg\text{-}SCH_3$, which are organo-mercurial compounds (check this out with any competent chemist). They are also very similar in structure to methyl-mercury ($CH_3\text{-}HgCl$) and dimethyl-mercury ($CH_3\text{-}Hg\text{-}CH_3$), the latter which caused the highly publicized death of a University of Dartmouth chemistry professor 10 months after she spilled two drops on her gloved hand. We have synthesized $CH_3S\text{-}HgCl$ and $CH_3\text{-}Hg\text{-}CH_3$ in my laboratory and tested their toxicity in comparison to Hg^{2+}. As expected, they were both more toxic than Hg^{2+} and this data is available on the www.altcorp.com web-site. Therefore, the ADA President is badly misinformed on this issue. Additionally, I am amazed that the researchers at the ADA and NIDCR did not previously report on this obvious chemistry as I would imagine this is the kind of topic they should be addressing.

"Based on currently available scientific evidence, the ADA believes that dental amalgam is a safe, affordable and durable material for all but a handful of individuals who are allergic to one of its components. It contains a mixture of metals such as silver, copper and tin, in addition to mercury, which chemically binds these components into a hard, stable and safe substance." This is a totally wrong statement unless you underline the *"ADA believes"* and define how big is a *"handful of individuals"*. Sensible people want "believes" replaced with "knows" and a "handful" replaced with a "hard number". Amalgams emit dangerous levels of mercury and the ADA absolutely refuses to accept this fact or even to study the possibility. Otherwise, the ADA administrators seem to be unable to separate fact from fiction. Consider, if they wanted to destroy my argument on

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amalgam toxicity they would reference several solid, refereed publication showing that mercury is not emitted from dental amalgams---but they cannot do this with even one article. They always state the "estimate" is that a very, very, very small amount. Competent, well-informed researchers don't use the evasive language used in the ADA President's letter. They would state the amount is so many micrograms mercury released per centimeter squared amalgam surface area and a "handful of individuals" would be a percentage of our population! Lets look at the published literature.

First, careful evaluation of the amount of mercury emitted from a commonly used dental amalgam in a test tube with 10 ml of water was presented in an article entitled "Long-term Dissolution of Mercury from a Non-Mercury-Releasing Amalgam". This study showed that "the over-all mean release of mercury was 43.5 ± 3.2 micrograms per cm^2/day, and the amount remained fairly constant during the duration of the experiments (2 years)" (7). This was without pressure, heat or galvanism as would have occurred if the amalgams were in a human mouth. Further, research where amalgams containing radioactive mercury were placed in sheep and monkeys, showed the radioactivity collecting in all body tissues and especially high in the jaw and facial bones. (8,9). Another publication, from a major U.S. School of Dentistry, stated that solutions in which amalgams had been soaked were "severely cytotoxic initially when Zn release was highest" (13). Zn is a needed element for body health and is found in very low percentages in dental amalgams when compared to mercury and why mercury was not mentioned in the abstract of this publication baffles me. Why would the statement be true? Because Zn^{2+} is a synergist that enhances mercury toxicity! However, does this sound like amalgams are a safe, stable material? We have repeated similar amalgam soaking experiments in my laboratory and the results can be seen at www.altcorp.com. Cadmium (from smoking), lead, zinc and other heavy metals enhanced mercury toxicity as expected (this research is currently being prepared for publication).

The ADA claim that a zinc oxide layer is formed on the amalgams that decreases mercury release is true, if you don't use the teeth. The zinc oxide layer would be easily removed by slight abrasion such as chewing food or brushing the teeth. Further, my laboratory has confirmed that solutions in which amalgams have been soaked can cause the inhibition of brain proteins that are inhibited by adding mercury chloride, and these are the same enzymes inhibited in AD brain samples.

Further, mercury emitting from a dental amalgam can be easily detected using the same mercury vapor analysis instrument used by OSHA and the EPA to monitor mercury levels. Anyone who does not believe mercury is emitted from amalgams should consider doing the following. Have your local dentist make 10 amalgams using the same material he/she places in your mouth. Take these 10 amalgams to your nearest research university's department of chemistry or toxicology department and have them determine how much mercury is being emitted. For example, have them calculate how long it would take a single spill of hardened amalgam to make a gallon of water to toxic to pass EPA standards as drinking water. You will then have an answer from an unbiased, solid group of scientists who are trained to do such determinations. Also, remember the level of mercury they measure would not include the increase that would occur with amalgams

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in the mouth where chewing, grinding your teeth, drinking hot liquids and galvanism greatly increase the release of mercury. Since this approach can be easily done by anyone don't you think the ADA, FDA and other amalgam supporters would have this published by now if the level of mercury released was below the danger level?

Here is their attempt. According to an ADA spokesman he has "estimated" that only 0.08 micrograms of mercury per amalgam per day is taken into the human body. Applying simple math to this "estimate" of 0.08 micrograms/ day one would divide this amount by 8,640 (24 hours/day X 60 minutes/hour X 6 ten second intervals/minute) to determine the amount of mercury in micrograms available for a ten second mercury vapor analysis. Consider that somewhere between one-half to five-sixths of the mercury released would be into the tooth (that area of the amalgam that exists below the visibly exposed amalgam surface) and not into the oral air. In addition, some mercury in the oral air would be rapidly absorbed into the saliva and oral mucosa (mercury loves hydrophobic cell membranes) and also not be measured by the mercury analyzer. Further, as the mercury analyzer pulls mercury containing oral air into the analysis chamber, mercury free ambient air rushes into the oral cavity decreasing the mercury concentration. Taking all of this into account you can calculate that most mercury analyzers could not detect this "estimated" 0.08 micrograms/day level of mercury even if you had several amalgams. However, the fact is that it is quite easy to detect mercury emitting from one amalgam using these analyzers. Therefore, the "estimate" by this ADA spokesman is way to low. Also, if you gently rub the amalgam with a tooth-brush the amount of mercury emitted goes up dramatically. This is a test anyone can do and demonstrate to any group. The ADA spokesmen state that the mercury vapor analyzer is not accurate at determining oral mercury levels and they are quite correct. However, using this instrument would greatly underestimate the amount of mercury exiting the amalgam. The very fact that the mercury analyzer detects high levels of oral mercury strongly indicates the emitted amount of mercury is to high to be acceptable.

Mercury release from dental amalgams is also the reason OSHA has used this analyzer to make the dentists place unused amalgam in a sealed container under liquid glycerin. This is done so that the mercury vapors from the amalgams will not contaminate the dental office making it an unsafe place to work. This is also the reason the EPA insists that removed amalgam filling and extracted teeth containing amalgam material be picked up and disposed of as toxic waste. Apparently, the only safe place for amalgams is in the human mouth if you believe what the ADA believes.

"Amalgams have been used for 150 years and, during that time, has established an extensively reviewed record of safety and effectiveness." First, what other aspect of industry or medicine is still using the same basic manufactured material that they used 150 years ago? One has to ask the question as to what has hindered the progress of development of better and safer dental materials? Also, consider that in the early 1900s the average life expectancy of most Americans was about 50 years of age and most of them could not afford dental fillings. Fifty to sixty years is much less than the average age of onset of AD. Further, amalgams became more available to most working class Americans after World War II, or in the early 1950s. The greatest increase in the use of

amalgam occurred at about this time and these 'baby boomers are the great ongoing amalgam experiment'. They are now reaching the age where AD appears and have lived most of their lives carrying amalgam fillings. They also wonder what is causing their chronic fatigue as the physicians can find nothing systemically wrong with them. I would encourage all concerned to contact the health experts on the rate of increase of AD in the U.S.A. at this time. Consider the cost it will place on the taxpayer and how much we would save if we could even remove the exacerbation factors that might speed up the onset of AD. I must point out that the *"extensively reviewed record of safety"* mentioned in the ADA letter was mostly done by dentists and committees dominated by ADA dentists. Also, much of the "safety opinion" was developed long before words like Alzheimer's disease and chronic fatigue were commonplace. Further, these were "reviews" and not carefully documented studies based on scientific experimentation and done by unqualified dentists, not medical scientists. Dentists are not trained to do basic research, nor are they trained in toxicology. Furthermore, the ADA does have a vested interest in keeping amalgam use legitimate. The ADA was founded on using amalgam technology and participated in patenting and licensing amalgam technology. One has to question why there has not been a general outcry by the bulk of well-meaning dentists and their patients and this question should be addressed. The International Association of Oral Medicine and Toxicology, started by American & Canadian dentists, does adamantly disagree with the ADA on the issue of safety of dental amalgams and this organization has the mantra of "Show me your science" with regards to all dental issues.

The ADA, through state dental boards stacked with ADA members, has instigated a "gag order" preventing dentists from even mentioning to their patients that amalgams are 50% mercury. Dentists cannot state that mercury is neurotoxic and emits from amalgams and that the dental patient should consider this as they select the tooth filling material they want used. If a dentist informs a patient of these very truthful facts he will be consider not to be practicing good dentistry and his license will be in jeopardy. Attacking a person's freedom of speech because he is telling the truth and causing serious questions to be asked about the protocols pushed by a bureaucracy (the ADA) makes me seriously question the commitment the ADA has for the health of the American people. The negative stand taken by many state dental boards against even informing the patients about the mercury content of amalgams and the other filling choices they have does not speak well for the organized dental profession. What medical group would give a treatment to a patient without telling them of the risks involved?

"Issued late in 1997, the FDI World Dental Federation and the World Health Organization consensus statement on dental amalgam stated "No controlled studies have been published demonstrating systemic adverse effects from amalgam restorations."" My first comment would be to question "who staffed these committees and what percentage were connected to the ADA though the NIDCR or the FDA dental materials branch or other relationships?" We appear to have the foxes guarding the henhouse! Then I would again point out that "absence of proof is not proof of absence". I would then ask 'have any controlled studies been done and if not, why not?' If the ADA dentists insist on placing amalgams in the mouth, are they not required to show it is safe, not the other way around? Should not the ADA and others concerned push to require the

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FDA to prove amalgams are safe instead of totally ducking this issue. Go to the FDA dental materials web-site and try to find any evaluation of amalgam safety---you will not succeed. The dental branch of the FDA refuses to do a safety study on amalgams and this is shame on our government.

"the small amount of mercury released from amalgam restorations, especially during placement and removal, has not been shown to cause any...adverse effects." This increase in mercury exposure has also not been shown to be safe by proving it does not cause any adverse effects! Are we to believe this elevated exposure to a toxic metal is good for us? If one were in a building that caused the rise in blood/urine mercury that appears after dental amalgam removal, then OSHA would shut the building down. In fact, no study by the ADA or NIDCR has been completed that specifically and accurately addresses this issue. Yet, the ADA leads us to believe that additional exposure to toxic mercury from these procedures is not dangerous to our health. Mercury toxicity is a retention toxicity that builds up during years of exposure. The toxicity of a singular level of mercury is greatly increased by current or subsequent, low exposures to lead or other toxic heavy metals (12). Therefore, the damage caused by amalgams could occur years after initial placement and at mercury levels now deemed safe by the ADA.

Our ability to protect ourselves from the toxic damage caused by exposure to mercury depends on the level of protective natural biochemical compounds (e.g. glutathione, metallothionine) in our cells and the levels of these protecting agents is dependent upon our health and age. If we become ill, or as we age, the cellular levels of glutathione drop and our protection against the toxic effects of mercury decreases and damage will be done. This is strongly supported by numerous studies where rodents have been chemically treated to decrease their cellular levels of protective glutathione and then treated with mercury, always with dramatic injurious effects when compared to controls. Therefore, published science indicates that mercury toxicity is much more pronounced in infants, the very old and the very ill.

A recent NIH study on 1127 military men showed the major contributor to human mercury body burden was dental amalgams. The amount of mercury in the urine increased about 4.5 fold in soldiers with the average number of amalgams versus the controls with no amalgams. In extreme cases it was over 8 fold higher. Since the total mercury included that from diet and industrial pollution are we to expect that this 4.5 to 8 fold average increase in mercury is not detrimental to our health? Does this indicate that amalgams are a *"safe and effective restorative material"*? Is the public and Congress expected to be so naïve as to believe that increased exposure above environmental exposure levels is not damaging? Then why are pregnant mothers told to limit seafood intake when mercury exposure from amalgams is much greater? Then why is the EPA pushing regulations to force the chloro-alkali plants and fossil fuel plants to clean up their mercury contributions to our environment? Obviously, from this study most of the human exposure to mercury is from dental amalgams, not fossil fuel plants. Yet, the FDA lets the dental profession continue to expose American citizens to even greater amounts of mercury. They do this by refusing to test amalgam fillings as a source of mercury exposure. Also, remember that the amalgam using ADA dentists are a major contributor to mercury in our water and air through mercury leaving the dental offices, and even when we are cremated.

"The ADA's Council on Scientific Affairs 1998 report on its review of the recent scientific literature on amalgam states: "The Council concludes that, based on available scientific information, amalgam continues to be a safe and effective restorative material." and *"There currently appears to be no justification for discontinuing the use of dental amalgam."* What would you expect an ADA Council to say? The ADA, as evidenced in the current letter by the President of the ADA, only quotes and considers valid the published research that supports their desire to continue placing mercury containing amalgam fillings in American citizens. When were dentists trained to evaluate neurological and toxicological data and manuscripts? What is needed is an international conference where both the pro- and anti-amalgam researchers show up and present their data in front of a world-class scientific committee. I would challenge the ADA to line up their scientists and supporters to participate in such a conference. This could be held in Washington, D.C. so the FDA officials could easily attend. Perhaps we could persuade the FDA to sponsor such a conference. However, this is unlikely since a recent written request to have a conference to evaluate the safety of amalgams was rejected in a letter from the FDA and signed by three FDA/ADA dentists who presented the ADA line on this issue. Doesn't it seem a bit fraudulent to have FDA/ADA dentists deciding on whether or not a safety study should be done on mercury emitting amalgams being placed in human mouths with the blessing of the ADA? This does seem like a conflict in interest that Congress should address.

"In an article published in the February 1999 issue of the Journal of the American Dental Association, researchers report finding "no significant association of Alzheimer's disease with the number, surface area or history of having dental amalgam restorations." This research was lead by a dentist, Dr. Sax. It was submitted to the J. of the American Medical Association and rejected. It was then submitted to the New England Journal of Medicine and rejected. It was then published in the ADA trade journal, JADA, that is not a refereed, scientific journal. JADA is loaded with commercial advertisements for dental products. They even called a "press conference" announcing the release of this article! Calling a press conference for a twice-rejected publication that is to appear in a trade journal is playing politics with science at its worst! At this press conference two of the authors made unbelievable statements that were not supported by any of the data in the article and conflicted with numerous major scientific reports, including the 1998 NIH study (6). Some of these were high-lighted in the side-bars of the ADA publication. I would suggest that those concerned with this article visit Medline and look at the publication records of the two individuals who made these statements. Also, look at the three earlier excellent publications in refereed journals by some of the other authors showing significant mercury levels in the brains of AD subjects compared to controls (14a,b, 15). However, put a dentist in charge of the project and the data gets reversed!

Apply some common sense. The ancillary comments by some of the authors and the results of the JADA publication are in total disagreement with the vast majority of research published that looks at elevated mercury levels in subjects with amalgam fillings. For example, the NIH study on military men discussed above showed a very significant elevation of mercury in the blood that correlated with number of dental amalgams (6). Another recent publication demonstrated elevated mercury in the blood of living AD patients in comparison to age-matched controls (10). These studies clearly show that there should be increased mercury in your blood if you have amalgams and especially if you have AD and amalgams (6,10). Does not the brain have blood in it? This makes it a total mystery as to how could the authors of the JADA article not find elevated brain mercury levels in patient with existing amalgams and/or AD. Even cadavers have brain mercury levels that correlate with the number of amalgam fillings they had on death.

Further, if you are addressing the contribution of amalgams to brain mercury and AD wouldn't it be important to divide the AD and control subjects into those with and without existing amalgams on death? In the JADA article this was not done and represents a major research flaw! That this was not done also arouses suspicion. I participated in submitting a letter pointing out this flaw to editors of JADA but they refused to acknowledge the letter and did not publish our comments. It is my opinion that the entire situation around this singular supportive publication of the ADA position on amalgams, brain mercury levels and AD represents a weak attempt at controlling the mind-set of well-meaning dentists, scientists, physicians and medical research administrators. It definitely impedes honest scientific debate. It also explains the cavalier attitude of the ADA and NIDCR about elemental mercury exposure and toxicity when compared to the more serious approaches taken by the EPA and OSHA.

With regards to the JADA article summary that "no statistically significant differences in brain mercury levels between subjects with Alzheimer's disease and control subjects." Here I must quote Mark Twain on honesty, "There are liars, damned liars and statisticians." Comparing the level of mercury in the AD versus control alone using straight-forward statistics previously showed a significant difference on mercury levels in AD versus control subjects (14a,b, 15). However, there are anomalies, confounders and other factors that can be considered in this situation, especially if you don't like the initial results. This allows one to invoke a Bon-Feroni statistical manipulation. With Bon-Feroni you include the comparison of one pair of data (that may be statistically significantly different taken alone, e.g. mercury levels in the brains of AD versus control subjects) with several other pairs of data rendering the difference statistically insignificant. One known weakness of the Bon-Feroni treatment of several coupled pairs of comparisons is that one very likely will miss a single comparison that is significantly different, and clever people know this. It is my opinion that application of the Bon-Feroni manipulation is what happened in this JADA study that reversed the previous significance of the mercury levels in AD versus control brain previously reported. Research previously reported by some of the very same researchers involved in the JADA study consistently indicated that mercury levels were higher in AD versus age-matched control brains (14a,b, 15). Only when an ADA dentist became involved did the results change to being insignificant. I think the data used in this JADA article and funded by NIH needs to be re-evaluated by a different statistician if we are to ever really know if the mercury levels in the AD brains differed significantly from controls.

The letter from the ADA President then lists four publications as proof of amalgams having no statistically significant negative effects. Two of these were published in Scandinavian Journals, another was a review of the literature in a Dental Journal, and one was the JADA article mentioned above. Sweden is well known to have lead the world in the restriction and replacement of dental amalgams with non-mercury containing materials. Forces are pushing hard to get the use of amalgams accepted again in Sweden to eliminate this embarrassment to our ADA. The current situation in Sweden and some other European countries, Canada and Japan seriously questions the ADA contention of amalgam safety. What if people in Sweden become healthier without amalgams?

Additionally, the studies quoted by the ADA President were epidemiological studies. These are very complex as many confounders are included which make finding a statistically significant difference very difficult. So the results are negative, nothing found, and not surprising. However, they are in disagreement with numerous other similar reports and appear to be hand-selected to support the ADA position. One has to wonder, since the ADA President seemed to visit Swedish journals to support the ADA position, how he missed the research of the Nylander group in Sweden that showed increased mercury content in brains and kidneys of humans in relationship to exposure to dental amalgams (17,18). Also, the referenced studies in the ADA letter did not involve neurotoxicity, autism or neurological disease---which is the question at hand. Rather, they addressed fertility, reproduction and other systemic illnesses. Could not the ADA find references to focus on neurotoxiological studies? What about the 1989 study that showed elevated levels of mercury in 54 individuals with Parkinson's disease when compared to 95 matched controls (16)? Further, one ought to consider who was doing these touted ADA studies and any vested interest they may have in the outcome. I am also aware of studies done in the U.S.A. by major research universities that would disagree with the conclusions drawn by the ADA on this subject yet these articles are not considered in the ADA letter.

At the end of the last publication the quote *"Conclusions: No statistically significant correlation was observed between dental amalgam and the incidence of diabetes, myocardial infarction, stroke, or cancer."* How does this relate to an article published in the J. of the American College of Cardiology where the mercury levels in the heart tissue of individuals who died from Idiopathic Dilated Cardiomyopathy (IDCM) contained mercury levels 22,000 times that of individuals who died of other forms of heart disease? Where did this tremendous amount of mercury come from? Even a Bon-Feroni manipulation could not make this difference insignificant! Many who die of IDCM are well-conditioned, young athletes who drop dead during sporting events---and they live in locations and in economic environments where sea-food is not a dietary mainstay. Perhaps the victims of IDCM are within the ADA Presidents *"handful of individuals who are allergic to one of its components."*

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"The National Institute of Dental and Craniofacial Research is currently supporting two very large clinical trials on the health effects of dental amalgam. Studies underway for several years each in Portugal and the Northeastern United States involve not only direct neurophysiological measures but also cognitive and functional assessments." Do we really think that the NIDCR and associated ADA personnel are going to deliver up a conclusion to American parents saying "we put a mercury containing toxic material in your child's mouth that lowered his/her I.Q. and made him more susceptible to neurological problems in comparison to the children whom we selected to not get exposed to this toxic material"? It is my opinion that most bureaucracies don't have a brain or a heart, but they do have a very strong survival instinct. Therefore, the results presented from this study will likely follow previously ADA supported research, i.e. no significant results.

Since the NIDCR started this project only 4 years ago one has to ask why it took so long for them to get involved since the "amalgam wars" have been going on for scores of years? Was it the overwhelming amount of modern science showing mercury from amalgams being a major part of the daily exposure that forced their hand and they had to develop a defense? Would I trust the conclusions of this study without knowing who put it together and who did the statistics? Not any more than I trust the conclusions of the JADA article mentioned in ADA letter that stupendously concludes that mercury from dental amalgams does not get into the brain.

As was proven by the tobacco situation, trying to find any significant negative effect of one product (amalgams) related to any disease through epidemiological studies is very difficult and complex. To do this with mercury would be difficult because of the synergistic effect two or more toxic metals or compounds (e.g. cadmium from smoking) may have on the toxicity of the mercury emitted from amalgams. For example, one publication showed that combining mercury and lead both at LD1 levels caused the killing rate to go to 100% or to an LD100 level (12). An LD1 level is where, due to the low concentrations, the mercury or the lead alone was not very toxic alone (i.e., killed less than 1% of rats exposed when metal were used alone). The 100% killing, when addition of 1% plus 1% we would expect 2%, represents synergistic toxicity. Therefore, mixing to non-lethal levels of mercury plus lead gave an extremely toxic mixture! What this proves is that one cannot define a "safe level of mercury" unless you absolutely know what others toxicants the individual is being exposed to. The combined toxicity of various materials, such as mercury, thimerosal, lead, aluminum, formaldehyde, etc., is unknown. The effects various combinations of these toxicants would have is also not defined except that we know they would be much worse than any one of the toxicants alone. So how could the ADA take any exception, based on intellectual considerations, to my contention that combinations of thimerosal and mercury could exacerbate the neurological conditions identified with autism and AD? Autism and AD have clinical and biological markers that correspond to those observed in patients with toxic mercury exposure. Why would the ADA take this position? I personally feel like I have been in a ten year argument with the town drunk on this issue. Facts don't count and data is only valid if it meets the pro-amalgam agenda.

The ADA was founded on the basis that mercury-containing amalgams are safe and useful for dental fillings. This may have been an acceptable position in 1850. However, modern science has proven that amalgams constantly emit unacceptable levels of mercury. Especially as the average life span has increased from 50 to 75-78 years of age where AD and Parkinson's become prevalent diseases. The ADA can try to verify its position using selected epidemiological studies. But the bottom line is that amalgams emit significant levels of neurotoxic mercury that are injurious to human health and would exacerbate the medical condition of those individuals with neurological diseases such as ALS, MS, Parkinson's, autism and AD.

I am hoping that the ADA sent this letter to your committee and also placed it on the ADA web-site to indicate that they are now willing for a wide-open discussion to take place on the issue of dental amalgams. I, for one, would welcome a major scientific conference on this issue. The ADA should feel free to post my letter in response and address any issue they feel that I am mistaken about. However, in closing I urge your committee to push forward on the study of the potential dangers of mercury in our dentistry and medicines. This includes mercury exposures from amalgams, vaccines and other medicaments containing thimerosal. The synergistic effects of mercury with many of the toxicants commonly found in our environment make the danger unpredictable and possibly quite severe, especially any mixture containing elemental mercury, organic mercury and other heavy metal toxicants such as aluminum.

Sincerely,

Boyd E. Haley

Boyd E. Haley
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Department of Chemistry
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Mr. BURTON. Thank you, Dr. Haley.

You may rest assured that we are going to put as much information before them and—if you want to call it pressure—pressure them as much as possible to research all of this.

Dr. Amaral.

Dr. AMARAL. Mr. Chairman and members, my name is David Amaral and I am a professor of psychiatry and neuroscience at the University of California, Davis.

The last 3 years, it has been my great privilege to be the research director of a new clinical research experiment called the MIND Institute. MIND stands for Medical Investigation of Neurodevelopmental Disorders. I deliberately referred to the Institute as an experiment because of the unique way in which it came into being, the unique way in which it governs its research, clinical, and educational programs, and the unique focus on understanding the biological basis of autism and other neurodevelopmental disorders in order to discover treatments and ultimately cures.

Historically, parents of children with autism have been given little hope and frequently advised to institutionalize their child and move on with their lives. This option was unacceptable to four Sacramento-area fathers, all of whom had sons diagnosed with autism in the 1990's. Chuck Gardner, a general contractor, Rick Hayes, an investment management, Rick Rollens, former secretary of the California State Senate, and Lou Vismara, a cardiologist, joined forces to create the concept of developing a world-class research and treatment center devoted to understanding the biology of autism in order to find treatments for theirs and other's children.

These four dads approached the UC Davis health system with the idea of forging a unique partnership between a University medical center and parents of autistic children to develop an institute where families could bring their children for state-of-the-art one-stop diagnosis. Those children diagnosed with autism or other neurodevelopmental disorders would then become subjects for multidisciplinary research aimed at understanding the causes and medical ramifications of their disorders. Once the biology of autism was better understood, then the clinic would become the proving ground for new treatments that would be developed based on the new research findings.

The MIND Institute research program, since that time, has followed a number of parallel paths of development. It is important to point out that the Research Committee, which is charged with all decisions about research direction at the Institute, is made up equally of parents and senior scientists at UC Davis. The committee has agreed that the prime directives of MIND Institute research are to remain open to all possibilities of causality, to carry out rigorous research in a collaborative multi-disciplinary fashion, to carry out innovative and even highly risky research if there are potentially large payoffs, and to try and determine the critical path to understanding the biology of autism in order to develop treatments as quickly as possible.

The MIND Institute research program currently has four components. It has a UC Davis intermural program, and we are attempting to develop a critical mass of researchers and facilities at UC

Davis in order to carry out state-of-the-art multi-disciplinary research on autism and other neurodevelopmental disorders.

It is clear that certain forms of research and therapy will only be accomplished when an intimate relationship is established between the clinic and basic science. This is really the guiding vision of the MIND Institute.

We have an investigator-initiated grant program. It is important to note that more than half of all the research funds allocated to the MIND Institute have actually been distributed to researchers at other UC campuses and other research facilities internationally to carry out research on autism and neurodevelopmental disorders. This extramural program is guided, again, by the parent-oriented philosophy that it is more important to get the critical research accomplished quickly than get the credit for accomplishing it at a particular institution.

We also have targeted research initiatives. Funds have been allocated to carry out research in areas that are currently underrepresented or in need of immediate attention. The MIND Institute, for example, has launched a nationwide effort to investigate the potential relationship between vaccines and autism. I will say more about that in a moment.

Finally, we have a MIND Institute scholars program. A major impediment—and we have heard this today—to rapid progress to research on autism is the relatively small number of scientists and clinicians who have autism as their primary area of interest. To encourage young scientists to enter the field, the MIND Institute has funded pre-doctoral students and post-doctoral fellows throughout the University of California system. It is hoped that these MIND Institute scholars will be the future leaders of autism research.

Let me briefly highlight some areas of current and future MIND Institute research. The first I would like to mention is the biomarkers program.

One of the first grants funded by the MIND Institute was awarded to a team from the California Birth Defects Monitoring Program, who collaborated with Dr. Karen Nelson from the NIH and with investigators from the MIND Institute. We heard a little bit about this this morning.

The so-called blood spot study sampled the blood spots that are taken from all children born in California. The investigators sought to determine whether there might be abnormal levels of certain peptides in the blood spots of children who were later diagnosed with autism.

This highly risky—what some would call a fishing expedition—made the striking discovery that several peptides were elevated in children who later became autistic or mentally retarded, but were not elevated in children with cerebral palsy or normal control subjects. This has led to the suspicion that more sophisticated techniques might provide a diagnostic marker for those children who are susceptible to autism. Of course, the significance of this finding is that there is substantial suspicion that while autism has a genetic component which makes children susceptible to the disorder, they must encounter another factor—a so-called second hit—that brings on the autistic symptomatology.

While it is not clear what the second hit may be—we have heard that many parents and others are concerned that it might be childhood vaccination or environmental contaminants—regardless of the precise identity of the second hit, if susceptible children could be detected at birth or before, once the causative agents are determined, these children could be protected from exposure. Therefore, finding a biomarker of autism is the highest priority of the MIND Institute research program.

One strategy is to employ the power of the Human Genome Project. In January 2001, the MIND Institute announced that it was allocating $1 million to develop a new neurodevelopmental genomics laboratory. The laboratory aims to identify a genetic profile or fingerprint of those children who may be vulnerable to autism. The goal of this program is to have an accurate diagnostic test that will be used to evaluate all children at birth, like the children are currently tested for Phenylketonuria.

A second initiative has been our vaccine-autism link research. As initially described by Mr. Rick Rollens in testimony to this committee on August 3, 1999—and we have heard much about this today—there is strong suspicion among parents that one ideology of autism of a child is associated with child vaccinations. While many organizations have been hesitant to take on this issue, the MIND Institute considered this to be a fundamental area for immediate action. If there is an identifiable culprit in existing vaccines that cause autism, then the removal of the agent or changes in vaccination policy could reduce future cases of autism.

In August 2000, the MIND Institute issued a request for proposal for research leading to precise scientific data on the potential links between vaccines and autism. With a private donation of $1.2 million and additional funds from the State of California, the RFP was advertised nationally and throughout the UC system and several grants have already been funded to carry on this research.

Another area of research is on the epidemiology of autism. The California State Legislature commissioned the UC Davis MIND Institute to carry out an evaluation of the factors that have led to the nearly 300 percent increase in the number of clients with autism in the regional center system and allocated $1 million for this effort. The principal investigator of this study is Dr. Robert Byrd in our Department of Pediatrics.

The overarching goal of this study is to determine whether factors such as in-migration or diagnostic shift can account for some of the increase in clients with autism. If you can discount some of these factors, then it has to be something else and we will look at those factors as well. The study team has been assembled. The field work is planned for September through December of this year. The analysis and reporting of results are slated for June 2002.

Another important area of work is what we call the autism tissue program. Much of the progress that has been made in the understanding of Alzheimer's Disease has come from the neuropathological and molecular biological analysis of post-mortem brain tissue. Literally hundreds of thousands of brains have been evaluated through recruitment at Alzheimer's research centers throughout the United States. In contrast, fewer than 40 autistic brains have been subjected to post-mortem analysis.

While it is clearly a very difficult issue that requires utmost sensitivity and compassion, progress in the understanding of the biology of autism will rely on the acquisition of well-preserved brain tissue from autistic patients. So to facilitate the goal of acquiring and distributing this resource, the MIND Institute has joined forces with the autism tissue program, sponsored by the National Alliance for Autism Research and Autism Society of America Foundation, to carry out the nationwide campaign to make parents and families aware of the need for tissue donations and to develop an efficient acquisition network that will allow optimal use of this precious resource.

And the last area I wanted to mention is a recently announced international meeting for autism research. There is currently no national or international meeting that brings together all scientists carrying out research in autism. The MIND Institute has joined with Cure Autism Now and the National Alliance for Autism Research to launch the first international meeting for autism research in San Diego on November 9 and 10 of this year. This meeting will encourage presentations of all types of research dealing with any aspect of biological basis of autism or experimental approaches to treatment.

It is expected that this meeting will contribute to increasing the awareness of new research findings and should foster new areas of research as well as new collaborative efforts.

So to summarize, the MIND Institute has quickly established a multi-component research program that is designed not only to help the children of today but those of the future. First, we are building a strong local infrastructure that will be uniquely capable of carrying out translational research on autism. Patients will not only be diagnosed in the clinic, but will become subjects for research. Once new findings lead to new treatments, the clinic will be the proving ground for these approaches. And once a new treatment is proven, it will be distributed to institutions worldwide for implementation.

Second, at the same time as research is carried out in Sacramento, the MIND Institute will support innovative research throughout California and eventually, with adequate fundraising, throughout the world.

Third, in addition to our own efforts, we will partner with other advocacy and research groups, including the NIH, to foster efforts that must be carried out through a concerted effort.

Through building a strong research team and collaborating nationally and internationally, it is my hope that we will ultimately understand and defeat autism. In the meantime, the MIND Institute will do everything in our power to treat children who are currently afflicted and strive to prevent new cases in the future.

Thank you very much.

[The prepared statement of Dr. Amaral follows:]

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Testimony provided by David G. Amaral, Ph.D.
Beneto Foundation Chair and Research Director of the M.I.N.D. Institute

To

Committee on Government Reform, House of Representatives
Honorable Dan Burton, Chairman
April 25, 2001

HISTORY

It is estimated that as many as 20 percent of the population is affected by a neurodevelopmental disorder such as autism, fragile X syndrome, cerebral palsy, Tourette's syndrome, attention deficit disorder and dyslexia. While estimates have ranged widely, recent epidemiological studies indicate that as many as 1 in 150 children are afflicted with autism or one of the autism spectrum disorders such as Asperger's syndrome. In California alone, eight children a day, diagnosed with autism, are added to the Department of Developmental Services system. The financial cost of providing lifelong care for each of these children is estimated to be approximately $2 million, i.e., a total of over $5.8 billion to provide care for all currently diagnosed individuals. And each year greater numbers of children are being diagnosed with autism, not only in California but also throughout the United States.

Although the financial costs are staggering, the emotional costs to families are even greater. Families are burdened with the daily care of children with autism and are concerned about their long term well being. The cause(s) of autism is(are) unknown. And there are currently few effective medical treatments for the disorder. Most heartbreaking are the cases of autism, in which seemingly normally developing children between 18 and 24 months of age experience severe regression, impacting their social, communication and cognitive skills. These children experience loss of speech and normal cognitive functions, coupled with occasionally violent tantrums as well as immunological, gastrointestinal and sleep disorders, leaving parents desperate for answers and treatments.

Although first recognized in 1943, there has been no large-scale, coordinated effort to find the cause(s), and eventual cure(s), for autism. Historically, parents of children with autism have been given little hope and frequently advised to institutionalize their child and move on with their lives. This option was unacceptable to four Sacramento area fathers, all of whom have sons diagnosed with autism in the early 1990's. Chuck Gardner, a general contractor, Rick Hayes, an investment treatment center devoted to understanding the biology of autism and other neurodevelopmental disorders in order to find increasingly better treatments and eventually cures for their own and other children.

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Mr. BURTON. Thank you, Dr. Amaral.

Dr. Miller.

Dr. MILLER. Thank you, Mr. Chairman.

Thank you for inviting me to this congressional hearing. I do so in my capacity as an epidemiologist who has worked for 22 years in the Public Health Laboratory Service in the United Kingdom on vaccine-related issues, with specific expertise in studies relating to vaccine safety.

For clarification, I should say that the PHLS in a non-governmental public body whose role is to provide a national capability for the diagnosis, surveillance, and prevention of communicable disease and the provision of independent advice about the control of communicable disease to help professionals and the Department of Health. The remit of the Immunization Division—which is part of the PHLS—of which I am head, is the national surveillance of immunization programs, including the safety and efficacy of vaccines that are in routine use.

Together with statistical colleagues in the PHLS and other academic institutions, over the years I have conducted a number of epidemiological studies designed to investigate various putative adverse events after different vaccines, including MMR, DPT, and more recently oral polio virus vaccine. These are referenced in my CV.

In some of these studies, evidence of a causal link between a specific adverse event and a vaccine has been found, and risks as rare as 1 in 10,000, 1 in 22,000, and even 1 in 143,000 doses have been detected. In other studies of possible adverse events, the results have been entirely negative. This is the case with the epidemiological studies I have conducted related to the postulated link between MMR and autism. Similar negative findings have been found in other work conducted elsewhere on the potential epidemiological link between MMR and autism.

These epidemiological studies have been designed to test the hypotheses implicit in the case reports and population trends in autism that Wakefield and others have interpreted as evidence of a causal link with MMR vaccine. The published evidence cited—some parents of autistic children say that the onset of symptoms in their child first occurred shortly after MMR, that prior to MMR their child was developing normally, that the onset of behavioral regression associated with MMR is typically accompanying by bowel symptoms, and that there has been an epidemic increase in the prevalence of autism which coincides with the introduction of MMR vaccine.

The studies I shall describe have been designed specifically to test the hypotheses that are implicit in these observations. I think it is disingenuous of Dr. Wakefield to say that he has inferred no hypotheses. I think it is also disingenuous of Dr. Spitzer to say that the study I was involved with was essentially a hypothesis-generating study. It was specifically testing a prior hypothesis that was derived from Wakefield's paper in the Lancet where the evidence that is put forward for an association between MMR and autism is the onset of regressive features or other behavioral disturbance shortly after MMR.

In brief, the summary of the findings of the various epidemiological studies—which are described in detail in my written submission to this committee with full references—are as follows.

There is no evidence that the onset of autistic symptoms is more likely shortly after MMR vaccine than at any other time. Indeed, new evidence which is shortly to appear from my colleagues and myself in a vaccine journal shows that there is no evidence that MMR vaccine increases the likelihood of autism at any time after vaccination.

Children with autism are no more likely to have received MMR vaccine than normal children. The introduction of MMR as a routine immunization for children in the second year of life has not been associated with a step-up increase in the incidence of autism.

When analyzed by birth cohort, there is no correlation between MMR uptake and prevalence of autism. I recognize that the Wakefield hypothesis has now moved on and has evolved—possibly under pressure of these epidemiological findings—but it is important to remember that the published work of Wakefield and others in relation to the putative link has been tested in the studies I have just described the findings of.

Most importantly, the final finding I will describe and show you the data from the study which is not yet published, there is no epidemiological evidence to suggest the emergence of a new syndrome of autistic enterocolitis associated with the use of MMR vaccine.

As I said, this latest finding, which I think is most pertinent here in relation to the postulated existence of this characteristic regressive autism with autistic enterocolitis—I would like to present the results of this later study here.

If it is true that vaccine-attributable cases typically present with developmental regression and bowel symptoms, then the proportion of such cases should have increased since the introduction of MMR. That is a logical conclusion and a logical inference from the hypothesis that is implicit in the data Dr. Wakefield has shown.

To test this hypothesis, my colleagues and I have updated our 1998 study of prevalent autistic cases in the North Thames Region of England by carrying out a further survey in 2000, 2½ years later. The prevalence data of the more recent birth cohorts shows that the rise in the early 1980's and early 1990's has now levelled off with no significant increase in prevalence in birth cohorts from 1993 onward.

The current prevalence rate is about 1 in 350 to 1 in 400 children. That is a high rate. And I would like to make it clear at this point that I do not in any way believe that this is a condition which should not attract substantial amounts of funding. We need to find the etiology and we need to find effective treatments.

However, the question of whether there has been an epidemic increase or whether that prevalence was there all the time but has only been recognized with appropriate diagnosis and referral mechanism I think is open to question. Certainly, my colleague, Professor Brent Taylor, who is a consultant community pediatrician, is of the opinion that the rise we had seen prior to 1993 was due to improve recognition and referral of cases rather than a real rise. I think the fact that it has flattened off since 1993 is consistent with that interpretation of the data.

However, the main purpose of this updated study was to test whether there has been an increase in the proportion of cases with regressive features and bowel symptoms associated with MMR.

[Slide presentation.]

Dr. MILLER. This shows that amongst children—there were 500 children in this survey—of children with regression—we concentrated specifically on children with regression and bowel symptoms. You can see there the portion of children with regression categorized by whether they had ever had MMR or indeed any measles-containing vaccine, whether they had that vaccine prior to parental concern—those are the cases that could possibly be caused by the vaccine, they were normal until they had thee vaccine—or whether they had the vaccine after parental concern. You can see that there is no significant difference in the percentage of cases with regression by MMR status.

A similar analysis done of the percentage of cases with bowel symptoms by MMR status again shows no significant difference between those three categories of autistic children—no MMR, MMR before onset, or MMR after onset.

Looked at another way, if we look at the percentage of cases with regression by year of birth, going from 1979 up to 1998—and remember that we introduced MMR in the UK in 1998, so in the middle there—you can see there has been no change in the proportion of cases with regression by year of birth.

Similarly, there has been no change in the cases of bowel symptoms by year of birth. Neither did we find that there was any characteristic bowel features in association with the use of MMR vaccine, constipation and diarrhea. These results are currently being submitted for publication.

In conclusion, in my view, the available epidemiological evidence, both from the United Kingdom and elsewhere, does not support a link between MMR and autism of the nature and frequency implicitly postulated by Wakefield and others and the basis of their published work so far. I recognize that the hypothesis has now evolved and moved on. Indeed, it provides strong grounds for rejection of the hypothesis that MMR is responsible for the reported rise in autism and that such cases are characterized by behavioral regression accompanied by bowel symptoms.

Clearly, no epidemiological study could prove that MMR vaccine never causes autism, however rarely. In this regard, epidemiologists are no different from any other scientist in that proof of a negative is impossible.

As with all epidemiological studies of any putative adverse event, the existence of a rare, idiosyncratic causal association cannot be entirely excluded. However, the existence of such a putative association between MMR vaccine and autism is at present entirely speculative.

Thank you.

[The prepared statement of Dr. Miller follows:]

Written testimony to the Congress of the United States House of Representatives Committee on Government Reform: Hearing on "Autism – Why the increased rates? A one year up-date".

Dr Elizabeth Miller
Epidemiologist and Head of the Immunisation Division
Communicable Disease Surveillance Centre
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Introduction

Thank you for inviting me to submit written testimony to the congressional hearing on autism, in particular the issue of whether the condition may be caused by MMR vaccine. I do so in my capacity as a medical epidemiologist who has worked for 22 years in the Public Health Laboratory Service on vaccine-related issues, with specific interest and expertise in studies relating to vaccine safety. The Public Health Laboratory Service (PHLS) in England and Wales is a non-governmental public body, equivalent to the UK National Health Service in terms of its funding and relationship to the Department of Health. The role of the PHLS is to provide a national capability for the detection, diagnosis, surveillance and prevention of communicable diseases. It consists of a network of some 50 public health laboratories in England and Wales which provide a national diagnostic and reference service, together with the Communicable Disease Surveillance Centre (CDSC), which is responsible for surveillance and epidemiological research. CDSC provides independent advice both to health care professionals and to the Department of Health, and epidemiological support for the investigation and control of outbreaks. It also takes a lead role in the training of health professionals in the epidemiology and control of communicable disease. The specific remit of the Immunisation Division of CDSC, of which I am the Head, is the national surveillance of immunisation programmes, including surveillance of vaccine uptake, disease incidence, immunity levels in the population and the safety and efficacy of vaccines that are in routine use.

Together with statistical colleagues in the PHLS Statistics Unit and the Department of Statistics at the UK, Open University, I have conducted a number of epidemiological studies designed to investigate various putative adverse events after different vaccines, including MMR vaccine, DPT (diphtheria/pertussis/tetanus) vaccine and oral polio virus vaccine. In some of these studies, evidence of a causal link between a specific adverse event and a vaccine has been found, with risks as rare as 1 in 10,000 doses [1] , 1 in 22,000 doses [2] and 1 in 143,000 doses [1] being detected, while in studies of other possible adverse events the evidence has been entirely negative. The latter has been the case with the epidemiological studies I have conducted relating to the postulated link between MMR and autism [3,4,20]. Epidemiological studies by others on this issue have also been negative [5,6,7,8].

These epidemiological studies have been designed to test the hypotheses implicit in the case reports and population trends in autism that Wakefield and others have interpreted as evidence of a causal link with MMR vaccine. The evidence cited by proponents of the hypothesised causal link is as follows: some parents of autistic children say that the onset of symptoms in their child first occurred shortly after MMR vaccine; that, prior to MMR vaccine, their child was developing normally; that the onset of behavioural regression associated with MMR vaccine is typically associated with bowel symptoms; that there has been an "epidemic" increase in the prevalence of autism which coincides with the introduction of MMR vaccine.

Summary of the epidemiological findings

In brief, the summary of the findings of the various epidemiological studies that have been designed to test the hypothesis that there is a causal association between MMR and autism, based on the epidemiological evidence of the type cited by Wakefield, is as follows:

1. There is no evidence that onset of autistic symptoms is more likely shortly after MMR vaccination than at any other time
2. There is no evidence that MMR vaccine increases the likelihood of autism at any time after vaccination

3. Children with autism are no more likely to have received MMR vaccine than normal children
4. The introduction of MMR as a routine immunisation for children in the second year of life has not been associated with a step up increase in the incidence of autism
5. When analysed by birth cohort, there is no correlation between MMR uptake and prevalence of autism
6. MMR vaccine does not change the age at onset of autism
7. There is no epidemiological evidence to suggest the emergence of a new syndrome of "autistic enterocolitis" characterised by the presence of behavioural regression accompanied by bowel symptoms associated with the use of MMR vaccine.

The scientific rationale of the studies that have been mounted to test the hypothesis that there is a causal association between MMR vaccine and autism is given below, together with a brief overview of their results. Clearly no epidemiological study could prove that MMR vaccine never causes autism, however rarely. In this regard epidemiologists are no different from any other scientist in that proof of a negative is impossible. However, the available data do allow rejection of the hypothesis that MMR is responsible for the reported rise in autism and that such cases are characterised by behavioural regression accompanied by bowel symptoms.

Basis of the hypothesised link between MMR and autism

The postulated link between MMR and autism is not based on inherent biological plausibility, such as might derive from a scientifically coherent body of published work, but has been inferred from two observations. First, anecdotal parental reports that the onset of behavioural disturbance in a previously normal child was acute and occurred shortly after MMR vaccine - the temporal association being apparently so clear that the parent has a personal conviction that MMR is responsible [9,10]. The development in such cases of a characteristic bowel condition in association with the behavioural disturbance has also been postulated [9,10]. Second, that there has been a very substantial increase in prevalence of (diagnosed) autism both in the USA and the UK which, according to Wakefield, coincides with the introduction of MMR [11].

Clearly, these two observations do not constitute scientific evidence, but taken together they do allow clear and testable hypotheses to be formulated. These are as follows: A) that there is a higher than expected incidence of autism cases with onset shortly after MMR and B) that there is a close temporal correspondence between autism prevalence and MMR uptake by birth cohort. Were it to be established that there is a correlation between MMR uptake and autism prevalence, this would be consistent with the hypothesis but would not constitute proof of a causal association. However, evidence that they were not correlated would favour rejection of a causal association. Because of the magnitude of the increase in (diagnosed) autism, if B is true then MMR must now be causing the majority of cases of autism. Furthermore, if Wakefield's proposition is true that vaccine-attributable cases have a characteristic presentation, typically developmental regression with the subsequent appearance of bowel symptoms, then this would lead to an ancillary hypothesis, C, that the proportion of cases with regression and bowel symptoms should have increased markedly since the introduction of MMR vaccine.

These hypotheses are quite distinct from the hypothesis of whether MMR might cause autism at any time after vaccination, and/or that just an occasional case of autism is caused by the vaccine. As far as I am aware, no epidemiological or virological evidence has been published which would lead to such hypotheses. Indeed it would be impractical to test a hypothesis of whether MMR vaccine could ever cause autism in extremely rare circumstances, as with any other putative very rare adverse event that is not exclusively vaccine-related.

Review of the relevant epidemiological evidence

To date, two studies [3, 8] have been specifically designed to test hypothesis A. In the Taylor et al study [3], of which I was as co-author, we investigated the following risk periods after MMR or any measles-containing vaccine for evidence of an increased incidence of onset of various markers of autism: intervals of 2, 4 and 6 months for onset of regression (the median interval in the Wakefield paper being 7 days range 1 day – 2 months), intervals of 6 and 12 months for parental concern and intervals of 12 and 24 months for diagnosis. The epidemiological method (the case series analysis method) that we used in our study was discussed in my earlier written testimony to the Congressional Hearing that took place in April 2000. With one exception, (consistent with a chance effect), all 13 other relative incidence estimates were not significantly different from one. We also looked for evidence that age at diagnosis differed between groups vaccinated before 18 months, after 18 months, or never vaccinated. If hypothesis A is true, then it would be expected that there would be a difference in age at onset by vaccination exposure. There was no evidence of such an effect.

In the subsequent Lancet correspondence on our paper, it was suggested that age at diagnosis is prone to bias because of delays in diagnosis (presumably based on irrelevant factors such as speed of referral) and that a similar analysis based on age at first parental concern would be more reassuring [12]. We therefore tested the hypothesis that age at first parental concern was affected by vaccine exposure, namely MMR before or after 15 months of age, or never vaccinated, on the subset of 244 cases with onset of parental concern between 15 and 48 months. We chose this earlier exposure since with the 18 month cut-off, onset of parental concern pre-dated vaccination in many more cases than did age at diagnosis. This new analysis was negative, p value for F test 0.61; the parameter estimates expressed as fold-differences in geometric mean ages were : vaccinated before 15 months over unvaccinated 0.96(95% CI 0.86-1.09); vaccinated after 15 months over unvaccinated 0.94 (0.84-1.06). These additional analyses are reported in [13].

In the recent IOM commissioned review of the epidemiological evidence relating to the postulated link between MMR and autism (by Stoto et al) it was suggested that our findings with respect to hypothesis A were inconclusive apparently because they were dependent "on the investigator's ability to precisely date both the receipt of the vaccine and the onset of symptoms" (page 38 of the commissioned review). The authors then go on to state that "Medical records are sometimes available to document the former" implying that there is a high level of uncertainty about the accuracy of the immunisation data in our study. This is a wholly mistaken view. In the UK, we have excellent computerised immunisation records held at district health authority level and, as should have been clear from our paper, immunisation records were found for virtually all (in fact all but two) study children. Information on the system whereby readily accessible and accurate information is available on immunisations given to UK children can be found in references 14 and 15. With respect to the ability to date onset of autism, Stoto et al stated that "the onset of developmental disorders in young children is difficult" (page 38) and that "because onset of autism is typically insidious, it is difficult to find a connection in time between vaccination and onset of autism" (page 23). As clearly indicated in our paper, we found statements in the notes of 374/498 (78%) of our study children that recorded age at first parental concern and, for all the subset of those with regression (n=110), age at which parents said they first noticed this. It is an essential part of the history taken by clinicians that they elicit, as accurately as possible, information on the age when parents first became concerned as this is highly relevant to establishing the diagnosis in children presenting with developmental delay. The onset of autism can only be determined by parental history, there being no objective retrospective test. If the view is taken that onset is too insidious to place any reliance on parental history, then in effect hypothesis A becomes untestable, notwithstanding the fact that the hypothesis under test derives specifically from parental information on age/timing of at onset. To adopt such a view would seem unfair and prejudicial.

If, nevertheless, the view is taken that hypotheses based on testing for increased incidence of onset in specific risk periods after MMR cannot be reliably tested, or indeed that MMR vaccine may cause autism with any induction interval, then an alternative hypothesis, D, can be generated, namely that receipt of MMR vaccine increases the subsequent risk of onset autism at any time after vaccination. In response to criticisms that our study design was unsuitable for investigating longer-term associations [16] we indicated that we had done new analyses of our data to accommodate longer induction times and that these analyses were negative [17]. The new findings are shortly to be published [4] and provide powerful evidence against the hypothesis that MMR vaccine causes autism at any time after vaccination.

The second study which has looked for evidence of an increase in onsets of autistic symptoms shortly after MMR vaccine used data from a general practice database – the Doctor's Independent Network (DIN) database which covers over one million patients in the UK and was set up in 1989 [8]. The hypothesis under test was that, if hypothesis A was true, then consultations among children with autism should show an increase in the 6 month period after vaccination compared to those in normal controls or in autistic children or normal children in the 6 month period prior to MMR vaccination. Periods of 2 months before and after MMR vaccination were also investigated. There was no evidence of any increase in consultation rates in either the 2 month or 6 month period after MMR in autistic children. The validity of the method was confirmed by showing a significant increase in consultations in the 6 months prior to the diagnosis of autism.

With respect to hypothesis B, there are a number of publications showing no association between introduction and uptake of MMR vaccine and prevalence [3,5,6] or incidence [7] of autism by birth cohort. While the trends in diagnosed autism in both the US and the UK suggest that there has been a substantial increase in recent years, this may simply reflect changes in diagnostic practice and the development of better information systems for identifying children with autism. My colleagues and I have now updated our earlier study of prevalent autistic cases in the North Thames region of England and the data for the more recent birth cohorts shows that since 1993 the rate has levelled off at around 2.7 per 1000 births. This finding is consistent with other recent population prevalence studies of autism and with the view that the reported rise in earlier birth cohorts results from improved ascertainment of cases [18,19].

As mentioned above, Wakefield seeks to lend support to the hypothesis that MMR cause autism by postulating the induction of a novel syndrome, "autistic enterocolitis" [9,10] thereby leading to testable hypothesis C. Among the objectives of the updated study in the North Thames region were i) to test whether there has been an increase in the proportion of cases with regressive features associated with MMR vaccination and ii) to test whether there was an association between bowel symptoms and MMR exposure. No evidence was found in support of either hypothesis. Specifically we found no differences in the proportions of children with regressive features or with bowel symptoms between those who had received MMR vaccine before their parents became concerned about their development (the putative cases caused by vaccination), those who received it only after first parental concern and those who had never received MMR or any other measles-containing vaccine. Furthermore, when analysed by birth cohort there was no evidence of a change in the proportion of autistic children with regression or bowel symptoms between 1979 and 1998, a 20 year period which encompassed the introduction of MMR vaccine in the UK in October 1988 as a routine immunisation of children in the second year of life. These results are currently being submitted for publication and were reported by my colleague Professor Taylor, Consultant Community Paediatrician at the Royal Free Hospital, at a recent meeting in the US [20].

Conclusion

In my view, the available epidemiological evidence, both from the UK and elsewhere, does not support a link between MMR and autism of the nature and frequency postulated by Wakefield and others. As with all epidemiological studies of any putative adverse event, the existence of a rare, idiosyncratic causal association cannot be entirely excluded. However, the existence of such a putative association is at present entirely speculative, there being no published data to suggest such a link.

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Mr. BURTON. Thank you, Dr. Miller.

Dr. Gershon.

Dr. GERSHON. Thank you, Mr. Chairman.

I am Dr. Michael Gershon, professor of anatomy and cell biology at Columbia University in New York.

Life is often unfair. The unfairness of the life dealt to autistic children, however, is so unfair that it defies comprehension. The mental elements of autism, which may sentence an innocent child to a life in virtual solitary confinement, are bad enough. To have to endure that sentence in gastrointestinal misery outdoes the trials of Job. The withdrawal from social contact that characterizes autism is so striking, moreover, that the abnormal behavior of afflicted children has historically tended to blind non-parental observers to symptoms from their gut, which in comparison, seem trivial.

Historically also, the possibility that there might be a pathophysiological link between the gut and the brain has not been considered, even by scientists who should have known enough to do so. Help to alleviate the gastrointestinal accompaniments of autism, therefore, has only recently been sought and investigation of the involvement of the bowel in autism begun.

Given that the involvement of the bowel in autism has not previously been studied, there is little that one can say right now about the causes of that involvement except that it is a topic worth considering. Certainly, the incidence of gastrointestinal problems in children with autism appears to be high and if one really looks for these conditions even higher. Professors Wakefield, Horvath, and their colleagues, therefore, have done a real service for patients and the biomedical community in publicizing the association of gastrointestinal abnormalities in autism.

At the start of a new field of research, such as the role of the gut in autism, one naturally formulates hypotheses that one can test. Hypotheses are very much a part of the scientific method. Unfortunately, it is relatively easy to construct an argument in support of a favored hypothesis, but an argument differs from evidence and should not be confused with it. An argument can serve to motivate hypothesis testing, but evidence is required for hypothesis confirmation.

The hypothesis that MMR vaccine is a cause of autism is supported at the moment by a well-crafted argument. There is, however, little or no hard evidence available to support that hypothesis. Furthermore, based on my understanding of gastrointestinal function and the nature of the blood brain barrier, I believe that it is unlikely that the hypothesis, as originally formulated by Wakefield and others, that MMR causes autism is correct.

The hypothesis that MMR is causally related to autism, which has been associated with Dr. Wakefield, postulates that the attenuated measles virus component of the vaccine persists in the bowel of those vaccine recipients destined to manifest autism as a result of their vaccination. The persistent measles virus is thought to elicit an immune response that is then postulated to increase the permeability of the intestinal epithelium, giving rise to a "leak."

This leak enables toxic materials—in particular, opioid peptides—to be absorbed from the intestinal lumen. These toxins then enter the bloodstream and are carried to the developing brain. The so-called rogue peptides, which are derived from the gut, cross the blood-brain barrier and damage the developing brain, giving rise to autism.

The evidence that measles virus actually persists in the bowel is controversial. The idea that measles virus persists has been recently been supported by Drs. Wakefield and his collaborator, Dr. O'Leary, with data derived from sensitive molecular biological techniques, which suggest that the virus is present in the bowel, but in very low copy numbers.

These data are still largely unpublished, and the findings have not yet, to my knowledge, appeared in a peer-reviewed journal. Other investigators have not been able to reproduce the molecular observations. Furthermore, test samples containing coded amount of measles RNA from cultured cells and from transgenic mice—which express the human measles virus—that were sent to Dr. O'Leary by Dr. Michael Oldstone were not read with the effectiveness needed to support the claims of low copy numbers of virus persisting in the gut of vaccinated individuals with autism.

Oldstone has concluded that the record of performance would not be acceptable for certifying a clinical laboratory. The virological support for the hypothesis of measles virus persistence, therefore, is not established and cannot be considered so until it is independently confirmed.

The data supporting the next step—the leak of toxic opioid peptides into the body from the lumen of the bowel—is scanty at best. Urinary observations of such are unreliable.

The thought that inflammation damages the epithelial lining of the bowel, causing its permeability to increase, is plausible. On the other hand, there is no reason that a leak in the gut should be a one-way leak. Nor is there any explanation as to how a leak could be specific so as to let only some molecules through and not others of the same size and shape pass through.

No movement of peptides or proteins from the tissue fluid to the intestine has been detected in autism or as a result of MMR vaccination. Protein-losing enteropathy has not been reported to be associated with autism, nor has it been reported to be a sequela of MMR vaccination in any significant number of people.

On the other hand, if the bowel were to be permeable in a size manner so that the large molecules of the body do not get out, then small molecules from the gut would go both ways through the proposed hole. That would cause massive malnutrition and malabsorption in the patients, which has not been reported.

So the absence of a telltale protein-losing loss or a failure of absorption in patients en masse with autism and in recipients of MMR vaccine thus suggests that the postulated leak of the gut admitting opioid peptides does not indeed occur. To paraphrase Sir Arthur Conan Doyle in Sherlock Holmes, the failure of these things to occur and the failure of absorption is the dog that did not bark. The postulated leak of the bowel is thus unlikely to occur or to be significant.

The idea that opioid peptides or other toxins enter the body from the bowel and cause autism overlooks another filter that is in place to remove them, and that filter is the liver. Everything the gut absorbs goes first to the liver as a consequence of the circulation. There is no evidence that MMR damages the liver. The postulated opioid peptides, therefore, would have to be absorbed in overwhelming amounts to overcome the ability of the liver to remove them. The liver is exceedingly good at removing opioids. There is no other toxicity noted in organs and the fact that the liver is there and is normal in patients with autism suggests that this postulated barrier is not overcome.

Finally, once the presumptively toxic peptides—if they ever could—overcome the barriers of the intestinal epithelium and the liver, which does not seem likely, the blood-brain barrier remains. That barrier is constituted by special vessels in the brain and it ought to be impenetrable to opioid peptides or other toxins. How these so-called toxins get across is unknown. One molecule that is large that does get across is leptin, which is a natural hormone, but it has its own transporter. No such molecules are known. So for a gut-derived peptide to be a cause of autism, one has to assume that a miracle occurs to cause the blood-brain barrier to open, like the Red Sea did for Moses and the Israelites during the exodus from Egypt.

Finally, there is no reason to assume that MMR is the only—or even the most likely—reason for an association between gastrointestinal disease to be associated with autism. The nervous system of the gut, the enteric nervous system, resembles the brain both structurally and chemically, and is known to share its fate in other conditions, including Alzheimer's and Parkinson's diseases.

It seems reasonable, therefore, to postulate that the incidence of gastrointestinal symptoms in children with autism is high because autism is a disease with manifestations in the gut as well as in the brain. Alternatively, a brain that functions abnormally because of autism may cause the bowel to function abnormally. Similarly, if there is a problem in the bowel, it can disturb the brain.

Let me tell you, Mr. Chairman, as I prepared for this talk, I became painfully aware of the kinds of problems that can happen in the bowel as the brain is disturbed. [Laughter.]

In summary, therefore, I think that there are alternative explanations for much of this and that the preponderance of evidence and the nature of the function of the gut, liver, and blood-brain barrier combine to indicate that it is unlikely that the hypothesis associated with Dr. Wakefield that MMR vaccine causes autism is correct. The idea that the measles virus persists in the gut of vaccinated individuals is supported only by data that is controversial and has not been confirmed.

The proposal that the bowel leaks due to measles virus persistence and absorbs opioid peptides or other toxins assumes a one-way leak. Since leaks are intrinsically not one-way, but holes in a barrier, body proteins or ions would be expected to flow out and no such movement has been detected in MMR or autism.

The hypothesis that toxins are absorbed does not take filtration by the liver into account or explain why gut-derived peptides are not removed.

Finally, it does not explain why peptides can get through the blood-brain barrier to cause autism and there are alternatives

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which are more plausible that can explain the association of GI malfunction in autism that have nothing to do with MMR.

In closing, I would just like to say that I sympathize tremendously and empathize with patients with autism and their parents. But it may be counterproductive for patients with autism, their parents, and for the whole population to devote energy and resources single-mindedly to the pursuit of a single theory of autism, when that theory might be false. The effort diverts scarce resources from avenues that might be needed and productive and should be devoted to this terrible condition.

Thank you.

[The prepared statement of Dr. Gershon follows:]

Testimony to the Congressional Oversight Committee on Government Reform

4/25/01

Michael D. Gershon, M.D.

Abstract

The preponderance of evidence and the nature of the function of the gut, liver, and blood brain barrier combine to indicate that it is unlikely that the hypothesis, associated with Dr. Andrew Wakefield, that the measles-mumps-rubella vaccine (MMR) causes autism is correct. The idea that measles virus persists in the gut of vaccinated individuals is supported only by data that is controversial and has not been confirmed. The proposal that the bowel "leaks" due to measles virus persistence and absorbs opioid peptides or other toxins assumes a one-way "leak". Since "leaks" are intrinsically not one-way valves, but holes in a barrier, body proteins and or ions would be expected flow out of the postulated "leak" into the gut; no such movement has been detected due to MMR or autism. The hypothesis that toxins are absorbed in autism does not take filtration by the liver into account and explain why gut-derived peptides are not removed as they circulate through the liver, which is not damaged in autistic patients. The hypothesis that peptides that are absorbed from the gut enter the brain to cause autism fails to explain how these can pass through the blood brain barrier, which would be expected to be impenetrable to them. Alternatives exist that explain the association between gastrointestinal malfunction and autism that have nothing to do with MMR.

Introduction: The gastrointestinal tract and autism.

Life is often unfair. The unfairness of the life dealt to autistic children, however, is so unfair that it defies comprehension. The mental elements of autism, which may sentence an innocent child to a life in virtual solitary confinement, are bad enough. To have to endure that sentence in gastrointestinal misery outdoes the trials of Job. The withdrawal from social contact that characterizes autism is so striking, moreover, that the abnormal behavior of afflicted children has historically tended to blind non-parental observers to symptoms from the gut, which in comparison, seem, to them, trivial. Historically also, the possibility that there might be a pathophysiological linkage between gut and brain, has not been considered, even by scientists who should have known enough to do so. Help to alleviate the gastrointestinal accompaniments of autism, therefore, has only recently been sought and investigation of the involvement of the bowel in autism begun (12, 20).

Given that the involvement of the bowel in autism has not previously been studied, there is little that one can say right now about the cause(s) of that involvement except that it is a topic worth considering. Certainly, the incidence of gastrointestinal problems in children with autism appears to be high and is, if one looks for these problems, even higher (12, 18, 20). Wakefield, Horvath, and their colleagues, therefore have done a real service for patients and the biomedical community in publicizing the association of gastrointestinal abnormalities and autism.

The hypothesis that measles-mumps-rubella (MMR) vaccine is a cause of autism

At the start of a new field of research, such as the role of the gut in autism, one naturally formulates hypotheses that one can test. Hypotheses are very much a part of the scientific method. In the privacy of one's home or laboratory, moreover, it is fair to

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formulate hypotheses on the basis of very little evidence, although even then it is best that there be a good reason for selecting hypotheses to be tested with actual experiments. Unfortunately, it is relatively easy to construct an argument in support of a favored hypothesis, but an argument differs from evidence and should not be confused with it. An argument can serve to motivate hypothesis testing; evidence is required for hypothesis confirmation. The hypothesis that the measles-mumps-rubella (MMR) vaccine is a cause of autism is supported, at the moment, by a well-crafted argument. There is, however, little or no hard evidence available to support that hypothesis; furthermore, based on my understanding of gastrointestinal function and the nature of the blood brain barrier, I believe that it is unlikely that the hypothesis that MMR causes autism is correct.

The hypothesis that MMR is causally related to autism, associated with Dr. Andrew Wakefield, postulates that the attenuated measles virus component of the vaccine persists in the bowel of those vaccine recipients destined to manifest autism as a result of their vaccination. The persistent measles virus is thought to elicit an immune response from the host that is then postulated to increase the permeability of the intestinal epithelium, giving rise to a "leak". This "leak" enables toxic materials, in particular opioid peptides, to be absorbed from the intestinal lumen. These toxins then enter the bloodstream and are carried to the developing brain. The "rogue" gut-derived peptides cross the blood-brain barrier and damage the developing brain, leading to autism. The toxins of intestinal origin can either do the damage themselves, or they might accentuate a genetic tendency to acquire autism.

Persistence of measles virus in the bowel

The evidence that measles virus from the MMR vaccine persists in the bowel is controversial. The initial immunocytochemical support for that persistence was challenged because of the strong possibility that the antibodies that were thought to demonstrate measles antigen also recognize endogenous body proteins. The idea that measles virus persists has subsequently been supported, by Dr. A. Wakefield and his collaborator, Dr. J. O'Leary, with data derived from sensitive molecular biological techniques, which suggest that the virus is present in the bowel, but in low copy numbers. These data are still largely unpublished, and although the observations have been presented by Dr. Wakefield, the findings have not yet, to my knowledge, appeared in a peer reviewed journal. Other investigators have not been able to reproduce the molecular observations; furthermore, test samples containing coded amounts of measles virus RNA from cultured cells and from transgenic mice (which express the human measles virus receptor and thus can be infected with measles virus) sent to Dr. O'Leary by Dr. Michael B.A. Oldstone were not read with the effectiveness needed to support the claims of low copy numbers of measles virus persisting in the gut of vaccinated individuals with autism. Oldstone found "…a lack of reliability and reproducibility for low gene copy numbers in MV [measles virus]-infected tissues and cells…" Oldstone also noted that "…there is questionable specificity as, on occasion, non-infected control tissues/cell have been recorded by O'Leary's laboratory as positive for MV". Repeated tests of the same RNA were sometimes read differently by the O'Leary laboratory on sequential trials. Oldstone has said that this record of performance would not be acceptable for certifying a clinical laboratory. The virological support for the hypothesis of measles virus persistence is therefore not established and cannot be considered so until it is independently confirmed.

The intestinal "leak"

The data supporting the next step, the "leak" of toxic opioid peptides into the body from the lumen of the bowel is scanty at best. The presumed detection of such peptides in the urine by means of the technique of high pressure liquid chromatography (which is commonly used by commercial laboratories for patients with autism) is flawed by the existence of many different compounds under the peaks of the chromatographic tracings.

No abnormal gut-derived peptides have yet been shown by sequence analysis to be present in the urine of autistic children. The thought that inflammation damages the epithelial lining of the bowel causing its permeability to increase is plausible. On the other hand, there is no reason why a "leak" in the gut should be only a one way "leak". Nor is there any explanation as to how a "leak" could be specific so as to let only some molecules and not others of the same size, shape, and charge pass through.

Peptides do not cross cell membranes; therefore, peptides larger than 2-3 amino acids cannot go through cells and the small peptides that do so, are carried by specific transporter molecules. The postulated "leak" therefore, has to involve movement of peptides between cells, the so-called "paracellular" pathway. This pathway, however, has no directional selectivity. Molecules that can go from the lumen to the tissue fluid can also go from the tissue fluid to the lumen. If the 'leak" is really large, it constitutes an "extracellular" pathway. No movement, however, of peptides or proteins from the tissue fluid to the intestine has been detected in autism or as a result of MMR vaccination. If the presumed "leak" were large enough to permit peptides to enter the body in significant amounts, then body proteins would be expected to move simultaneously in the opposite direction into the lumen of the bowel. This movement would, if it occurred, lead to the condition known as protein losing enteropathy. Protein losing enteropathy has not been reported to be associated with autism; neither has it been reported to be associated with MMR vaccination.

Conceivably, a hitherto unknown phenomenon might be postulated, in which the inflammation elicited by the putative persistent measles virus causes tight junctions, the "plugs" that seal off the space between epithelial cells, to admit peptides of only a certain size to pass through them. Such a size-selective lesion might permit opioid peptides to move into the body, but not permit the larger body proteins to move out. If that were to occur, however, then the patients in whom it was happening would develop severe signs of malnutrition. The sodium gradients and other molecular transport mechanisms upon which the bowel depends for its absorptive activity rely on tight junctions to do their job. There is no way that a size-selective hole in the gastrointestinal epithelium could pass molecules as large as peptides and not the much smaller molecules and ions that the epithelial cells transport. The absence of either a telltale protein losing enteropathy or a failure of absorption in patients with autism and in recipients of MMR vaccine thus suggests that the postulated "leak" of the gut, admitting opioid peptides does not occur. To paraphrase Sir Arthur Conan Doyle, the failure to observe either a protein losing enteropathy or a failure of absorption is the dog that didn't bark. The postulated "leak" of the bowel is thus unlikely to occur or to be significant.

Filtration of blood by the liver

The idea that opioid peptides or other toxins enter the body from the bowel and cause autism overlooks another filter that the body has in place to guard against this type of calamity. That filter is the liver. Everything that the gut absorbs into the blood goes to the liver by way of the portal circulation before it can flow to the brain. Blood is simply directed by the anatomy of the vessels to circulate that way. The liver thus gets to sample the blood before other organs and is highly developed to remove spurious peptides and other toxins. It is well known that transient toxicity of the brain occurs when the liver is damaged; moreover, opiates, in particular, are detoxified in the liver. There is no reason to assume that the livers of patients with autism are abnormal, and if they were, the patients would manifest jaundice and other stigmata of liver disease, which they do not. There is also no evidence that MMR damages the liver. The postulated opioid peptides, therefore, would have to be absorbed in such overwhelming amounts that they would overcome the ability of the liver to remove them. That possibility is far-fetched; moreover, the difficulty in demonstrating the existence of the postulated toxins indicates that they could not possibly be absorbed in overwhelming quantities. There is also no other toxicity noted in organs other than the presumptively affected brain, as would be anticipated if non-detoxified toxins were being absorbed in significant amounts.

The blood brain barrier

Once the presumptively toxic peptides from the gut overcome the barriers of the intestinal epithelium and the liver, neither of which seems particularly likely, there remains the blood-brain barrier. This barrier, constituted by specialized cerebral capillaries, evolved to keep the brain from being disrupted by events in the periphery just like those postulated in the pathogenesis of autism. It is therefore necessary to assume that the putative opioid peptides or other toxins penetrate a barrier that should be impenetrable to them. One large molecule that does get across the blood-brain barrier is the natural hormone produced by fat cells, leptin. This molecule can traverse the blood-brain barrier because cerebral capillaries have a highly specific transport system to carry leptin across. Leptin does not resemble opioid peptides in any way. The gut-derived molecules, therefore, cannot utilize the leptin transporter, and would have to induce some other transporter to be genetically created for their benefit, resemble some unknown endogenous molecule that has an unknown transporter that carries them, or cause the blood-brain barrier to break down. There is no evidence for any of these implausible events. The gut-derived peptide as a cause of autism thus has to assume that a miracle occurs to cause the blood-brain barrier to open, like the Red Sea did for Moses and the Isrealites during their exodus from Egypt.

Alternatives to MMR as the cause of a gut-brain association in autism

Finally, there is no reason to assume that MMR is the only, or even the most likely, reason for an association between gastrointestinal disease and autism. There is instead good reason to believe that a disease that affects the function of the brain might also affect the function of the bowel. The nervous system of the gut, the enteric nervous system, resembles the brain (structurally and chemically) and is known to share its fate in other conditions, including Alzheimer's and Parkinson's diseases (8, 9). It seems reasonable, therefore, to postulate that the incidence of gastrointestinal symptoms in children with autism is high because autism is a disease with manifestations in the gut as well as in the brain. Alternatively, a brain that functions abnormally because of autism might, by way of the enteric nervous system, distort the function of the bowel. Certainly, almost everyone has experienced the nervous diarrhea or other anxiety related gastrointestinal symptoms that occur when the stressed brain sends unwanted messages to the bowel.

The gut can also affect the brain in the absence of toxins and a set of improbable occurrences. In order to function normally, the enteric nervous system must accurately monitor conditions in the lumen of the bowel (11). The intraluminal acidity, concentrations of nutrients, salts, and pressure all affect digestion and have to be sensed. Similarly, the brain must also detect intraluminal conditions, in order to modulate the activity of the enteric nervous system, trigger vomiting, stop feeding, and initiate other appropriate behaviors. Despite the requirement for both gastrointestinal and brain detection of luminal stimuli, no nerve fibers actually penetrate the gastrointestinal epithelium and expose themselves to luminal contents (15). All sensing of luminal conditions by the enteric nervous system and central nervous system, therefore, is accomplished across the barriers of the epithelial layer of the gut. This transepithelial sensation is accomplished by a process of chemical transmission, which is not dissimilar to chemical neurotransmission. The gastrointestinal epithelium contains specialized sensing cells, which function as transducers (1-5, 7, 10, 13, 14, 17). Luminal stimuli activate these cells, which respond by secreting chemical messengers into the wall of the bowel. These chemicals, in turn, stimulate sensory nerve fibers in the lamina propria.

The best characterized of the epithelial transducers is the EC cell, which secretes serotonin in response to pressure (6).

Many autistic children have a profound abnormality of EC cell serotonin secretion, which is manifested in the high blood (platelet) serotonin level found in a majority of autistic patients. Virtually all of the serotonin in blood is stored in platelets (19). Platelets take up serotonin (16) but cannot synthesize it (19) and obtain essentially all of their serotonin from the gut (6, 19). The reproducible presence of high blood serotonin in autism confirms an abnormality of gastrointestinal function and suggests that the enteric nervous system is involved. This defect could be primary or secondary but there is no easy way to relate it to MMR. The brain can thus disturb the gut and the gut can disturb the brain; both might equally be abnormal for whatever the genetic reason for autism turns out to be

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Mr. BURTON. Let me just start off by saying that I know just a couple of things. No. 1, there is an epidemic. There is a huge quantum leap in the number of children that are autistic. That is irrefutable. That is No. 1.

No. 2, I know that my grandson, Christian, was a normal child starting to speak and doing everything that was normal and 1 day he got the DPT shot, he got the MMR shot, he got the Hepatitis B shot, the Polio shot, and the Marcus Influenza shot, and 10 days later he had those bowel problems, had chronic diarrhea, ran around hitting his head against the wall, flapping his arms, and he could not talk anymore.

That may be just a coincidence, but it happened. I saw it with my own eyes, so something happened. Whether it was the MMR shot or the mercury that was in these other vaccines or a combination of the two, I do not know. But I do know that hundreds of thousands of children in this country and around the world are suffering because of autism, and many of them are suffering from autism shortly after having received one or more of these vaccines.

Dr. Haley, you said that there was about a 10-fold occurrence of autism in children who had the mercury vaccines and the MMR. I am not sure exactly how you said it.

Dr. HALEY. I was not making any mention of the rate of autism.

Mr. BURTON. What were you saying?

Dr. HALEY. It is on the back page of the handout.

When you compare the toxicity against the bank of enzymes or against enzymes in a brain tissue, if you add the vaccines that do not contain thimerosal, they show the least amount of toxicity, essentially, very little at all.

Mr. BURTON. Right.

Dr. HALEY. If you use the same vaccine, only with thimerosal added as a preservative, they are tremendously much more toxic.

Mr. BURTON. You said about 10 times, did you not?

Dr. HALEY. I am being very conservative; 1 microliter of these vaccines will totally inhibit these enzymes. You can sometimes add 10 microliters of the non-thimerosal-containing vaccines and see just a few percent——

Mr. BURTON. You also said that similar things occurred with the MMR vaccine.

Dr. HALEY. We also measured the mercury level because some of the vaccines we received had been used a bit. We looked at the level of mercury. It fit what you would expect. There are low levels of mercury in the non-thimerosal-containing vaccines. There is some in all of them. The ones that had thimerosal added were quite high.

The MMR came across as if it had no thimerosal added. There was a small amount in there. I think it would be similar to those that had no thimerosal added. There was mercury in there, but not very much.

Mr. BURTON. There was mercury in the MMR vaccine?

Dr. HALEY. Yes, but a very small amount.

Mr. BURTON. But there was mercury in the vaccine?

Dr. HALEY. Yes, but the toxicity——

Mr. BURTON. Merck, when we called awhile ago, said that there was no mercury in the MMR vaccine. You are saying that there was a very small amount.

Dr. HALEY. Yes, we found it. I would want to do 20 of them before I came up with an average, but we did find a small amount of mercury. It was very tiny, though.

The MMR vaccine, unlike those vaccines without thimerosal, was very toxic. It was as toxic as if it had thimerosal in it.

Mr. BURTON. So would you say it was 10 times more toxic than a vaccine without thimerosal?

Dr. HALEY. I would say so, yes.

Mr. BURTON. Dr. Spitzer and Dr. Wakefield, I am sure you are squirming there. Would you like to make any kind of comment about what you just heard? [Laughter.]

Dr. WAKEFIELD. Generally, Mr. Chairman, or in specific relation? [Laughter.]

Mr. BURTON. The whole hypothesis of your research was pretty much trashed by the last two witnesses.

Dr. WAKEFIELD. I think Dr. Miller confuses inference with implication. She says that implicit in what we had written was a hypothesis. That, unfortunately, was her inference rather than our implication.

What we have written—and this is one of the earliest articles where we articulated a hypothesis—I am afraid this is in scientific jargon—the hypothesis hypothesized that autistic enterocolitis is an emergent, inflammatory bowel disease that follows a low-dose compound viral exposure. Basically, that this subset of autism with an inflammatory disease is an emergent form of inflammatory bowel disease that follows a very atypical pattern of viral exposure that requires not one virus but an interaction between viruses and possibly other things as well.

And we go on in that same paper—and I will not go into the details because it is too much scientific jargon—but it comes back very much to what Dr. Bradstreet was talking about. If the developing immune system is impaired in some way from developing an appropriate anti-viral response to exposure to mercury or other vaccines, if it is skewed in the wrong direction, then it may behave aberrantly in the face of a virus.

I am very happy to provide Dr. Miller with a copy of this paper and I will include one for your records.

Mr. BURTON. Thank you.

Dr. Spitzer.

Dr. SPITZER. I would first like to make a comment.

There has been implication about comparing benefits and costs or good and harm in this situation. The understandable zeal, as indicating in the Institute of Medicine report, of coming close to wiping out a disease and the sequela of measles through the measures that are being taken is a very laudable goal.

If we think, on the other hand, that say 10 percent only of autistic children are those in which we eventually find a link between the disease and that vaccine were the case, a conservative estimate is 150 children per 100,000 with autism—reducing it by 10 percent is reducing 15 near deaths, if you wish, in the community.

With respect to the other side of the coin, comparisons are almost always made, as I have read them recently in the literature, with no immunization at all as opposed to making the reference the best acceptable alternative, which is univalent measles vaccine. The grandchildren I have I want to have vaccinated, but with univalent unless it is clarified.

That would reduce in UK statistics, which I only give in a preliminary way—I was just looking at them last Friday for the first time—going from second to MMR meant a reduction of about 16 per 100,000 to usually zero or close to zero in developed countries like the UK. It really is about the same, even if only 10 percent of autistic children are affected.

That means it is important that we look at subsets, even small subsets. If we can prevent 10 percent of autism by a more judicious strategy of immunization, to that extent we will have balanced the ledger of harm.

Last, I would like to stress in my case, I call myself a worried agnostic. I do not know whether there is an association. I think the evidence leans slightly in the direction of supporting an association. Perhaps causation, but at least association. I only feel that I am involved in one cause, and that is the pursuit of truth through scientific, admissible science, even if it takes 4 or 5 years to get to the first step.

Mr. BURTON. Thank you, Dr. Spitzer.

Mr. Waxman, do you have some questions?

Mr. WAXMAN. Yes, I do.

Thank you, Mr. Chairman.

Dr. Wakefield, Marie McCormick is the Chair of the Institute of Medicine's Committee on Immunization Safety Review. She said at the press conference at the release of the report that the MMR vaccine is as safe as a vaccine can get.

How do you respond?

Dr. WAKEFIELD. That is a very interesting comment. It is rhetorical inasmuch—let me put it this way. When the vaccine was first put together in 1969, one of the concerns I had in particular was that of interaction of viruses one with another. It is called viral interference.

Mr. WAXMAN. Dr. Wakefield, we are limited to 5 minutes each, so I would really like a very terse and clear response.

Dr. WAKEFIELD. When the MMR was first put together, it was evident that the viruses interacted one with another. That was assumed to be a benign process. That was a major mistake, in my impression. I do not believe that when you put them together it is a benign process. It alters the outcome from the vaccine, it alters the immune response.

Mr. WAXMAN. Do you think the MMR vaccine is as safe as a vaccine can get?

Dr. WAKEFIELD. No, absolutely not.

Mr. WAXMAN. That is your view, but the Institute of Medicine is not the only organization that disagrees with you. Your work has also been scrutinized by the Medical Research Council and the American Academy of Pediatrics and none of them has found any evidence to support your hypothesis.

Dr. Miller, in your testimony, you demonstrate that the proportion of autistic children with regression or bowel symptoms has not changed over the period in which the MMR has been used in the UK and is also no different for children who have never had an MMR vaccination or those who developed autism after the vaccine.

What does that suggest about Dr. Wakefield's theory?

Dr. MILLER. I obviously do not want to put hypotheses into Dr. Wakefield's mouth. The hypothesis I would infer that should be tested on the basis of his suggestion of an autistic enterocolitis syndrome is that there should have been an increase in the proportion of such cases with regression and bowel symptoms associated with the use of MMR vaccine. I cannot find that in a large sample. I find that at variance with any inferences I might make about what I would expect to have happened on the basis of Dr. Wakefield's theories.

I therefore have to come to what I believe is a reasonable conclusion that my observation does not support his hypothesis.

Mr. WAXMAN. In other words, your new findings show that MMR is not linked to bowel syndrome and is not linked to autism. And this research, combined with the IOM report, really show that there is no evidence to support a causal connection between autism and MMR.

We have limited resources to devote to this cause. As a public health official and an epidemiologist, do you think that more resources should be devoted to investigating the MMR-autism connection? Or are there better places to devote our resources?

Dr. MILLER. As I said in my testimony, I think the question of what is the cause of autism—it is a common condition and we need effective treatments—is extremely important to answer. I think that there have already been quite a number of resources devoted to the question of MMR and autism, both looking at the evidence by expert committees plus individuals like myself doing as best we can with epidemiological studies. These have been uniformly negative.

As I said in my oral testimony, one cannot rule out a rare idiosyncratic response. However, in relation to what is the major cause of autism, I am firmly of the view that MMR has been excluded as a major cause of autism. Therefore, I do not think it would be profitable to—if you like—hijack the research agenda to concentrate on answering this question, which is derived basically from speculation and unsubstantiated and, as yet, still unpublished evidence in relation to MMR and autism.

Mr. WAXMAN. Thank you.

Dr. Gershon, an important part of Dr. Wakefield's theory, as I understand it, is that the measles virus persists in the gut. Yet from what I understand, no other scientist has been able to replicate Dr. Wakefield's findings of the persistence of measles virus in the gut. Moreover, I also understand that Dr. O'Leary, Wakefield's associate who does the looking for the measles virus, was tested to see if he could correctly identify measles virus in infected samples and he failed that test.

Do you know if that is correct? If so, can you explain the significance of this?

Dr. GERSHON. It is correct. And the significance of it is that the evidence we have heard—which is largely unpublished and is not supported or duplicated by other laboratories—is not adequate to support Dr. Wakefield's hypothesis. So the evidence that the persistence of measles virus goes on in the gut is simply unfounded at the moment.

Mr. WAXMAN. Mr. Chairman, I would like to ask unanimous consent if I could have another 5 minutes to pursue questions because I have a conflict and have to run to another meeting.

Mr. BURTON. Go ahead.

Mr. WAXMAN. Dr. Haley, your research demonstrates thimerosal inhibits enzyme activity and that demonstrates that the thimerosal, in your experience, is dangerous to the enzyme in the petri dish.

Don't we need to know how much thimerosal is in the vaccine before we know whether it is dangerous to a human being?

Dr. HALEY. Toxicity is always related to dose, but also size, the ability to clear it, the health of the patient, the metabolic status, if they were suffering from a spurious ailment it would be more toxic.

Mr. WAXMAN. So the research you are presenting today does not definitively answer the question of whether the amount of thimerosal in childhood immunizations is dangerous or not, does it?

Dr. HALEY. That it is dangerous?

Mr. WAXMAN. Yes.

Dr. HALEY. I think if you consider the aspect that we are dealing with multiple toxicities and exposures to mercury from a lot of different sources that adding an abundance of mercury to a child——

Mr. WAXMAN. My question, though, is whether the amount of thimerosal in the childhood immunizations is dangerous, the amount that is in there. There may be other exposures.

Dr. HALEY. The amount from the vaccine alone would probably be not enough by the data we have seen. But again, that would depend upon the health of the patient you are giving it to.

Mr. BURTON. Would the gentleman yield?

Mr. WAXMAN. Sure.

Mr. BURTON. Is there a cumulative effect of mercury——

Dr. HALEY. Yes.

Mr. BURTON. In other words, my grandson—and I appreciate you yielding—got nine shots. I think four or five of those shots he got on that 1 day contained mercury. They said that was 41 times what was normal.

Would that cumulative effect have an adverse impact?

Dr. HALEY. Absolutely.

Mr. BURTON. Did you hear that, Henry?

Mr. WAXMAN. What was that answer? [Laughter.]

Dr. HALEY. There are a lot of reports out there with infants that have been exposed to excess ethyl mercury generating compounds.

Mr. WAXMAN. Are you aware of an abstract study funded by NIH that looked at the blood mercury levels of full-term infants following the administration of thimerosal-containing vaccines?

Dr. HALEY. Yes, I am. My opinion on that is that blood mercury levels have been considered by many people not to be worth very much to the extent of mercury toxicity. It is a retention toxicity.

Mr. WAXMAN. I would like to read the conclusion of that abstract. "Low levels of mercury can be detected in the blood of some full-term infants following the administration of vaccines containing thimerosal. None of the blood mercury levels observed in the studied infants exceeded the most recently revised lowest level of maternal blood mercury considered to represent a potentially significant exposure to the developing fetus."

That seems to disagree with your testimony. That seems to be at odds with what you are saying.

Dr. HALEY. If anybody is saying they can look at the level of mercury in blood after a vaccination and then come to the assumption that this did no harm to that patient, I sincerely disagree with them.

Mr. WAXMAN. Does the research you have represented today prove that the mercury in vaccines causes autism?

Dr. HALEY. Absolutely not.

Mr. WAXMAN. In your testimony, you stated that infants cannot clear mercury from their bodies. But a recent study conducted by the University of Rochester testing mercury in infants found that mercury was detected in the infants' feces.

Don't these findings prove that infants can clear mercury from their bodies?

Dr. HALEY. I did not say they could not, I said that they could not do it as well. They have reduced bilary transport. It takes a while for that to develop. And from what I understand, they get the vaccination on the day they are born.

Mr. WAXMAN. Dr. McDougle, first I want to begin by commending you for the excellent work you are doing to advance our understanding of how to treat autism. Much of your attention is focused on determining the causes of autism, and that is important, but it is also important to help individuals and families who are suffering now.

I understand you are in the middle of a 5-year grant to develop medications to treat the symptoms of autism. Can you give us a preliminary assessment of the effectiveness of some of the medications you are studying?

Dr. MCDOUGLE. Yes. I would say that the first study we completed was with a medication called Risparidone. Although the blind has not been broken yet and we are not aware of who was on which placebo or drug, certainly a number of children have improved and benefited with particular improvements in the areas of aggression, self-injury, irritability, and I think has ultimately improved their quality of life.

Mr. WAXMAN. So some of them are working?

Dr. MCDOUGLE. Yes.

Mr. WAXMAN. Thank you very much, Mr. Chairman and my colleagues.

Mr. BURTON. I hope you did not miss the response from Dr. Haley on that one thing because we have asked this question of others when you were not in attendance, and that is that the mercury in the vaccines has a cumulative effect. If the child gets eight or nine shots in 1 day, as my grandson did, he is getting an exorbitant amount of mercury in one dose. In my grandson's case, 10 days later he was autistic.

Dr. Weldon.

Mr. WELDON. I want to thank all the witnesses. For me, personally, I am just trying to find out how we can direct our research funding better to try to get some answers to some of these questions.

Dr. Miller, you described the Public Health Lab as being a non-governmental public body. Do you get funding from the British Government, though?

Dr. MILLER. Yes, in the same way the National Health Service is funded by the British Government, but we are not an arm of government. Our relationship to the Department of Health and Government is the same as the UK National Health Service.

Mr. WELDON. Is all your funding from the government? Or does some of it come from other entities? Specifically, does any of it come from the pharmaceutical industry?

Dr. MILLER. Our core funding comes from the government. As with the National Health Service, researchers like myself apply for funding from research agencies, research funds from the Department of Health. I have no commercial interests in any vaccine company. I do not act as a consultant or an advisor to a vaccine company. I do, along with other individuals, have research funds for specific studies, largely clinical trials, from vaccine companies. I have not been sponsored from any of the work that I do on autism from vaccine companies.

I should say that in relation to the circumstances under which any funding comes from such commercial sources, the legal department of the Public Health Laboratory Service draws up a very stringent contract with the commercial company to ensure that there is total scientific independence of the PHLS in publication and interpretation of those results. This is a standard procedure for organizations such as the PHLS.

Mr. WELDON. So you are saying that the funding comes from the British Government and some of it does come from pharmaceutical companies, but you have these——

Dr. MILLER. A small amount for specific research projects.

I am also an advisor to the Medicine Control Agency, that is similar to the FDA. And as a requirement for that, we have a declaration of interest. Should members of the committee wish to see the funding I have received and for what purposes, then they are free to view that. I am not sure if it is on the MCA Web site.

So there is a full declaration of interest. The ability to provide independent scientific advice is scrutinized by the MCA in relation to the type of financial benefit that is received for research studies from companies. I have not been prevented from having any input over advisory matters in relation to the research funding that I have received.

I should say, it is a very small proportion of the total amount I have received for research studies.

Mr. WELDON. It would be very comforting to me if the PHLS would just spend $500,000 and try to recruit 50 kids with autistic spectrum disorder and gastrointestinal symptoms and just scope them and try to duplicate his findings. It is very little comfort to me, all these epidemiologic studies, because the hypothesis is not that MMR causes all forms of autism. If you are operating under the assumption that MMR causes a small percentage of the cases of autism, then that may be very, very difficult to detect in an epidemiologic study.

If the British Government is all concerned about vaccination rates declining because of Wakefield's findings, why don't they just scope 50 kids? What is the problem?

Dr. MILLER. I would like to say first of all that you have put your finger on the nub of the question here. I think you have accepted that the epidemiological evidence has already excluded MMR as a common cause of autism. I said in my testimony that it is impossible epidemiologically to prove that it could never cause it.

So the question is, for how rare an event would you like a study to be set up to exclude or to find that sort of risk?

For the purposes of spending public money, if one has excluded MMR as a frequent cause of autism——

Mr. WELDON. I would like to interrupt you, because I have a limited amount of time.

He came in my office and showed me the pictures. I have spoken to people. I am an internist. These kids have florid inflammatory bowel disease. Why can't somebody duplicate this study?

We have this poor, lone guy coming here constantly, year in and year out. [Laughter.]

And Dr. O'Leary, might I say, is the guy who identified Herpes Simplex Type A. He came here to the NIH and all of the people at NIH supposedly dismissed it as being invalid and ultimately it was found to be true that Herpes Simplex Type A causes carposisarcoma. O'Leary is a very, very reputable scientist.

Why can't we repeat O'Leary's data?

Dr. MILLER. First of all, we have to wait to see the virological findings published in a peer-review journal. As Dr. Gershon said, we have not yet seen those.

The Public Health Laboratory Service, as I mentioned, its remit is the national diagnosis, surveillance, and prevention of communicable disease. Autistic enterocolitis, as far as I am aware, is not demonstrated to be a communicable disease, nor indeed to result from vaccination.

Now whether there is a syndrome called autistic enterocolitis which has distinctive pathological features, fenotific presentation is another question. And maybe gastroenterologists, in combination with autism experts should be looking at that. It is not a question for PHLS.

Mr. WELDON. The responsibility to duplicate his work is not something that your department would——

Dr. MILLER. Our responsibility would relate to the question, if there is such a syndrome, Is there evidence that it is associated with MMR?

Analyses of that has come to the conclusion that no—whether or not there is such a syndrome, whether or not it has relevance to the current prevalence of autism is another question, and academic institutions with expert gastroenterologists and autism experts may indeed be looking at this.

I would say the Medical Research Council has funded a large study to look at the question of etiology of autism and what the risk facts are to try to throw some light on it, but it is not a question related to vaccines or communicable disease.

Mr. WELDON. I have some questions for Dr. Gershon.

This is not published, but I have been told by some of the people doing research in treating children with autism that a substantial percentage of them do have elevation in their liver function tests.

If that were published and proved to be true, would that affect your opinion regarding this theory of these neuroactive peptides?

Dr. GERSHON. It would affect my opinion if the elevation of liver function tests were such that it would affect the ability of the liver to act as a filter.

Mr. WELDON. So you would want to see very significant elevations, not very mild elevations.

Dr. GERSHON. For example, jaundice.

Mr. WELDON. You would want to see jaundice?

Dr. GERSHON. I would like to see some evidence that the liver is failing in its job as a filter. I would also like to have some evidence that material is moving from into the gut from the body. I would like to see some evidence that the intestinal epithelial barrier is failing. And I would like to see some mechanism to get whatever toxins are so-called absorbed through the blood-brain barrier.

Mr. WELDON. Regarding the blood-brain barrier, it was brought to my attention that a Dr. Connolly published in the Journal of Pediatrics in May 1999. Maybe you might be familiar with this study. The title of the article was "Serum Autoantibodies to Brain in Landau-Klefner Variant, Autism, and Other Neurologic Disorders." It was basically showing antibodies to brain endothelium.

Are you familiar with that study at all?

Dr. GERSHON. I have seen the study.

Mr. WELDON. That does not affect your opinion at all about this theory? That study has no impact?

To me, that study suggests that there could be a possible link and explanation here. I am not saying there is, as a scientist myself. I think I would want to see more research. But you dismiss the theory outright, and that study suggested to me that in some of these kids there may actually be a breakdown in the blood-brain barrier.

Dr. GERSHON. That study did not demonstrate a breakdown in the blood-brain barrier. It showed autoantibodies. That is a different issue.

The existence of antibodies—it could be an autoimmune mechanism, I guess, is what you are implying—that helps to break the blood-brain barrier down. There could be a lot of things.

Every step along the way, an improbable event could happen. But there are a lot of steps along the way.

I would like to direct your attention to two other points. One part of my testimony and one further one.

I pointed out that there are alternative mechanisms by which to explain the association between bowel disease and autism. One need not postulate a set of improbable mechanisms to get toxins into the brain. The bowel and the brain communicate by other means. The fact that both are involved in autism is, to me, established. As I said at the outset, Professor Wakefield is to be commended for publicizing that.

On the other hand, I do not think it is established that the reason for the link is MMR. The bowel has many mechanisms of affecting the brain and the brain the bowel. The same disease, autism, can give rise to symptoms in both places.

The other thing, in regard to what you said about scoping—if the British Government or our Government were to scope a lot of children and find inflammation in the bowel, I would expect that they would in fact find that. Nobody, to my knowledge, is quarrelling with the aspect of what Dr. Wakefield has published, which is that some children with autism have in fact inflammatory bowel disease. That is not in contention. What is in contention is that resulted from MMR and that there is persistent measles virus in it, that what they detect is not just passenger leftover from the vaccine that is not real virus.

It is very hard to show that. And Professor O'Leary—I am not saying he is not a good molecular biologist. I think he is an excellent molecular biologist. But when asked with coded samples that were sent to him by Michael Oldstone to show that he could detect these low copy numbers which are postulated, he did not pass the test. He identified successive samples differently on different occasions. He missed some diagnoses. When there were very large amounts of measles virus, he could detect it, as could everybody else.

And here we have a situation where other laboratories are trying to duplicate this finding of measles virus, and they are not doing it. Yet this laboratory has failed the test of coded samples to do it.

Mr. WELDON. Mr. Chairman, could we have Dr. Wakefield?

Mr. BURTON. Dr. Wakefield.

Dr. WAKEFIELD. I am sorry, I have to take issue with that. That is a complete misrepresentation of the data.

First, Dr. Gershon suggests that other people have looked in the intestine of these children for the detection of measles virus. No one has done that, to my knowledge. So the only laboratory that has looked in the intestinal biopsies of these children is Dr. O'Leary's laboratory. Other people have looked in the intestines of children with Crohn's Disease for evidence of measles virus, which we have suggested. Indeed, one of the people on the panel of the IOM presented data at the American Academy of Pediatrics last June showing that they had could identify measles virus genetic material in children with Crohn's Disease and some controls.

I want that to go on record. That has been presented.

So independently groups from Canada and from Japan have found measles virus in the intestines of children with inflammatory bowel disease.

The issue of the study with Michael Oldstone was not as it was portrayed. I am very, very concerned that Michael Oldstone should breach confidence of data that has not been presented in any forum, and has not even actually been finally analyzed. But in fact when they did analyze them, the only discrepancy was that there was no contamination at all, but a very, very, very low copy number of the virus, which the tacman PCR system—which Dr. O'Leary helped develop—detects the virus found that they might be able to detect it in two out of three samples.

This is merely a function of low copy viral detection. It is now a function of the ability of us to find viruses in vanishing small amounts with technology that is not available in Dr. Oldstone's lab. So the data have not been presented fairly, and I want that to go on record.

Mr. BURTON. Dr. Weldon, you can keep the time, but I want to make a comment or two because I have no more questions for the panel. Then I will let you conclude the questioning.

A lot of kids are ruined for life. I detect a close-minded attitude on something that is so important—not to one child, my grandson, but to hundreds of thousands of kids. Every 3 hours in California—it was every 6 hours just about a year ago—but every 3 hours in California, there is a new child with autism. Every 3 hours.

It is a horrible, horrible thing to have to live with, not just for the child but for the parents, the grandparents, and everybody else, not to mention the cost.

So we have some people that have a closed mind about various theories about this. I think this is a time for everybody to be open to almost any theory, if it is cost-effective, to look at it to see if it can be proved or disproved.

I want to tell you a story. Louis Pasteur was kicked out of the medical profession and ostracized for 17 years and then he was knighted. And it was because everybody had a closed mind.

I have a very good friend who lives in Australia. His name is Dr. Barry Marshall. I do not know if you have ever heard of him or not. But I went to Africa and I was in the jungles of Angola and I came down with a bug, I thought, because I could not eat anything or keep it down for 2 years. It was awful. So I went to gastroenterologists. I went to several of them. And they all said it was my nerves and strain on my body. They gave me Zantac and Prilosec and everything else under the sun.

Then I read this article about this guy named Barry Marshall. I think it was in one of the major publications. He was a scientist doctor from Australia. He said that the stomach problems in 90 percent of the people in the world was caused by a bacteria. Everybody said that a bacteria cannot live in the stomach.

He went and gave a speech to a symposium in Belgium. After he gave the speech—or right near the end—they literally started laughing at him because it was impossible for a bacteria to live in the lining of the stomach and he was crazy. So he went home and drank the bacteria—not unlike what Louis Pasteur did. He went home and drank it and got deathly ill and cured himself with the combination that he gave me.

I went down to see him after 2 years of suffering and he tested me. My doctor said I didn't have that. But I went to see him and he gave me this concoction of bismuth and antibiotics and something else. I took it for 2 weeks and I have not had a problem since.

But the close-minded doctors who were experts, who had all the answers, told me that I could not be cured, that I had to take these stomach pills for the rest of my life. All I can tell you is that we have a problem with kids that is humongous. It is going to affect the whole world if we do not do something because we are vaccinating kids all over the world. If mercury or the MMR vaccine or whatever it is is causing it, we need to find out and we need to find out pretty darn quickly.

For people to have closed minds when 1 out of 150 or 200 kids in Oregon or 1 out of 400 in the United States or 1 in 500 in the United Kingdom are coming down with autism is almost criminal. You ought to explore everything to find out what the answer is.

With that, I will shut up.

[Applause.]

Mr. BURTON. Dr. Weldon.

Mr. WELDON. I just have a couple of quick followup questions.

Dr. Wakefield, Dr. O'Leary came in my office and showed me his PCR data, all the different versions of that. I think he ran eight different types of tests. Why hasn't that been published yet? We have had Dr. Gershon point that out repeatedly that it has not been published. What is the problem?

Dr. WAKEFIELD. There is no problem. It is being presented for the first time at the American Gastroenterological Association in Atlanta in May. It has been peer-reviewed and we will see how that goes. But it is awaiting publication at the moment.

We have been asked to provide strain-specific sequencing. In other words, the acceptance is that the virus may well be there. I sat down with Michael Oldstone himself who said that he accepted that we found the virus. NIH's measles expert who came to troubleshoot this said that the virus is there. But the reviewers have asked for strain-specific sequencing. Those studies are being conducted at the moment and we will put those into the papers. It is an entirely reasonable question and one that we are answering.

Mr. WELDON. So you expect publication after that issue is decided?

Dr. WAKEFIELD. Once we have addressed that issue, yes.

Mr. WELDON. Just one more question for you, Dr. Miller.

Were you on the original panel that approved the MMR in England?

Dr. MILLER. No, I had no role in that at all.

Mr. WELDON. That is all I have, Mr. Chairman. Thank you.

Mr. BURTON. I want to thank you all very much. You have been very patient. You have been sitting for a long time. You have been very helpful.

We will submit all your statements and all your comments to the health agencies here. We will continue to fight on to try to find a solution to this problem, with your help.

Thank you.

We have one more witness who could not be with us tomorrow, Dr. McCormick from the Institute of Medicine. She is the chairman who did the report that we had heard about.

Dr. Weldon, you can stay for Dr. McCormick, I hope. She was the chairman of the committee that did the report that was recently released. I need you.

[Witnesses sworn.]

Mr. BURTON. Do you have an opening statement, Dr. McCormick?

Dr. MCCORMICK. Yes, I do.

Mr. BURTON. You are recognized.

STATEMENT OF MARIE MCCORMICK, MDSCD, CHAIR, COMMITTEE ON IMMUNIZATION SAFETY REVIEW, INSTITUTE OF MEDICINE, ACCOMPANIED BY WILLIAM COLGLAZIER, EXECUTIVE OFFICER, NATIONAL ACADEMY OF SCIENCES; AND SUSANNE STOIBER, EXECUTIVE OFFICER

Dr. McCormick. Good afternoon, Mr. Chairman and members of the committee.

My name is Marie McCormick. I am a professor and Chair of the Department of Maternal and Child Health at Harvard School of Public Health and I Chair the Institute of Medicine's Committee on Immunization Safety Review, which released its report on MMR Vaccine and Autism on Monday, April 23rd. I appreciate the opportunity to provide testimony to you based on the findings of this report. A copy of my testimony and the executive summary has been submitted for the record.

Dr. William Colglazier, executive officer of the National Academy of Sciences, and Ms. Susanne Stoiber, executive officer of the Institute of Medicine accompany me.

As I mentioned, two committee members are here, Dr. Steve Goodman and Dr. Constantine Gatsonis.

The genesis of this report was a December 1999 discussion between the CDC and the IOM regarding the need for an independent group to examine vaccine safety concerns. The CDC and NIH formally engaged the services of the Institute of Medicine in September 2000, which in turn appointed the committee in November 2000.

The committee is comprised of 15 members with expertise in pediatrics, immunology, neurology, infectious disease, epidemiology, biostatistics, public health, genetics, ethics, risk perception, and communication. To preclude any real or perceived conflicts of interest, committee members were subject to strict selection criteria that excluded anyone who had participated in research on vaccine safety, received funding from vaccine manufacturers or their parent companies, or served on vaccine advisory committees.

The committee is charged with examining three vaccine safety issues each year for 3 years. The committee was asked to assess the scientific plausibility of the safety concern, the significance of the issue in a broader social context, and to suggest appropriate actions. The first hypothesis the committee was asked to consider is the linkage between MMR vaccine and autism.

The MMR vaccine has been extremely successful in virtually eliminating measles, mumps, and rubella in the United States. Measles cases, for example, dropped from over 400,000 per year in the pre-vaccine era to only 100 in 1999.

Some are concerned, though, that the MMR vaccine might cause autistic spectrum disorders. These are incurable, permanent, and serious developmental problems in children and adults. Scientists generally agree that most cases of autistic spectrum disorders result from events that occur in the prenatal period or shortly after birth. However, concern arises about the MMR vaccine because autistic symptoms typically become more evident in the child's second year, about the same time the MMR vaccine is first administered.

A growing body of work has examined this subject. In a study published in the Lancet in 1998, researchers describe 12 children who developed behavioral problems, including autism, shortly after receiving the MMR vaccine. Since then, this group and others have further examined this potential relationship.

To evaluate the hypothesis on MMR vaccine and autistic spectrum disorders, the committee conducted an extensive review of the published, peer-reviewed scientific and medical literature. We held an open scientific meeting including a broad group of researchers and vaccine safety advocates. Finally, a working group of the committee conferred with parents of autistic children and vaccine safety advocates to discuss their concerns.

The committee concludes that the evidence favors rejection of a causal relationship at the population level between MMR vaccine and autistic spectrum disorders. The committee bases this conclusion on the following evidence: a consistent body of epidemiological evidence shows no association at a population level between MMR vaccine and autistic spectrum disorders; the original case series of children with autistic spectrum disorders and bowel symptoms and other available case reports are uninformative with respect to causality; biologic models are fragmentary; and there is no relevant animal model.

However, the committee notes that its conclusion does not exclude the possibility that MMR vaccine could in rare cases contribute to autistic spectrum disorders resulting in a very small number of affected children. This possibility arises because the epidemiological evidence lacks the precision to assess rare occurrences and the proposed biological models, although far from established, are nevertheless not disproved.

In its significance assessment, the committee considered the burden of measles, mumps, and rubella infections, the burden of autistic spectrum disorders, and the level of public concern. Measles, mumps, and rubella can lead to significant morbidity and mortality and treatment of these diseases is limited.

Outbreaks of measles, mumps, or rubella disease could easily occur now were MMR immunization rates to decline as a result of fears about MMR. Yet, because MMR vaccine is a mandatory vaccine that is administered to healthy children—in part, as a public health measure to protect others—the responsibility of the Government to ensure the safety of the vaccine is high. The burden of autism, an incurable and serious disorder, requires consideration of all possible etiologies. In addition, the level of public concern about MMR vaccine safety is high.

Because of the limitations of the evidence, the significant public concern surrounding the issue, the risk of disease outbreaks if immunization rates fall, and the burden of autism, the committee recommends that further attention be given to this matter.

Specific recommendations regarding policy review, research and surveillance, and communication follow.

In terms of policy review, the committee does not recommend a policy review at this time of the licensure of the MMR vaccine or of the current schedule and recommendations for administration of MMR.

The committee concludes that further targeted research on the possible contribution of MMR vaccine to autistic spectrum disorders in some children is warranted. For example: use accepted case definitions and assessment protocols for autistic spectrum disorders to enhance the precision and comparability of research results; explore whether exposure to MMR vaccine is a risk factor for autistic spectrum disorders in some children; explore whether measles vaccine-strain virus is present in the intestines of some autistic children; and encourage all who submit reports tot he Vaccine Adverse Event Reporting System about MMR vaccine and autism to provide as much detail and documentation as possible.

The committee heard from parents that obtaining unbiased and accurate information on the possible relationship between MMR vaccine and autistic spectrum disorder has been difficult. The committee recommends that governmental and professional organizations, CDC and the FDA in particular, review some of the most prominent forms of communication regarding the relationship between MMR vaccine and autism spectrum disorder. Direct input from parents and other stakeholders would be invaluable in conducting an evaluation of communication tools.

In its discussion of recommendations, the committee identified more general concerns that it could not adequately address in this report. It intends to address these in the future.

This concludes my oral statement and I would be happy to answer any questions.

[NOTE.—A copy of the Institute of Medicine publication entitled, "Immunization Safety Review," may be found in committee files, or obtained by calling the National Academy Press at 1–800–624–6242.]

[The prepared statement of Dr. McCormick follows:]

Immunization Safety Review
Measles-Mumps-Rubella Vaccine and Autism

Statement of

Marie McCormick, M.D., Sc.D.
Chairman of the Immunization Safety Review Committee
Institute of Medicine/National Academy of Sciences
and
Professor and Chair, Department of Maternal and Child Health
Harvard School of Public Health

before the
Committee on Government Reform
U.S. House of Representatives

April 25, 2001

Good morning, Mr. Chairman and members of the committee, my name is Marie McCormick. I am a professor and chair of the Department of Maternal and Child Health at Harvard School of Public Health. I chair the Institute of Medicine Committee on Immunization Safety Review, which released its report on Measles-Mumps-Rubella Vaccine and Autism on Monday, April 23. I appreciate the opportunity to provide testimony to you based on the findings of this report. A copy of my testimony and the Executive Summary have been submitted for the record. Dr. William Colglazier, Executive Officer of the National Academy of Sciences and Ms. Susanne Stoiber, Executive Officer of the Institute of Medicine accompany me.

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The committee is charged with examining three vaccine safety issues each year for 3 years. The committee was asked to assess the scientific plausibility of the safety concern, the significance of the issue in a broader social context, and to suggest appropriate actions. The first hypothesis the committee was asked to consider is the linkage between measles-mumps-rubella vaccine (MMR) and autism.

Study Background and Methodology

The MMR vaccine has been extremely successful in virtually eliminating measles, mumps, and rubella in the United States. Measles cases, for example, dropped from over 400,000 per year in the pre-vaccine era to only 100 in 1999.

Some are concerned though that the MMR vaccine might cause autistic spectrum disorders. These are incurable, permanent, and serious developmental problems in children. Scientists generally agree that most cases of autistic spectrum disorders result from events that occur in the prenatal period or shortly after birth. However, concern arises about MMR vaccine because autistic symptoms typically become evident in the child's second year—about the same time the MMR vaccine is first administered.

A growing body of work has examined this subject. In a study published in *The Lancet* in 1998, researchers describe 12 children who developed behavioral problems including autism shortly after receiving the MMR vaccine. Since then, this group and others have further examined this potential relationship.

To evaluate the hypothesis on MMR vaccine and autistic spectrum disorders, the committee conducted an extensive review of the published, peer-reviewed scientific and medical literature. We held an open scientific meeting including a broad group of researchers and vaccine safety advocates. Finally, a working group of the committee conferred with parents of autistic children and vaccine safety advocates to discuss their concerns.

Study Findings

Plausibility Assessment

The Committee concludes that the evidence favors rejection of a causal relationship at the population level between MMR vaccine and autistic spectrum disorders. The committee bases this conclusion on the following evidence:

- A consistent body of epidemiological evidence shows no association at a population level between MMR vaccine and autistic spectrum disorders.
- The original case series of children with autistic spectrum disorders and bowel symptoms and other available case reports are uninformative with respect to causality.
- Biologic models are fragmentary.
- There is no relevant animal model.

However, the committee notes that its conclusion does not exclude the possibility that MMR vaccine could in rare cases contribute to autistic spectrum disorders resulting in a very small number of affected children. This possibility arises because the epidemiological evidence lacks the precision to assess rare occurrences and the proposed biological models, although far from established, are nevertheless not disproved.

Significance Assessment

In its significance assessment, the committee considered the burden of measles, mumps, and rubella infections, the burden of autistic spectrum disorders, and the level of public concern. Measles, mumps, and rubella can lead to significant morbidity and mortality and treatment of these diseases is limited.

Outbreaks of measles, mumps, or rubella disease could easily occur now were MMR immunization rates to decline as a result of fears about MMR. Yet, because MMR vaccine is a mandatory vaccine that is administered to healthy children—in part, as a public health measure to protect others—the responsibility of the government to ensure the safety of this vaccine is high. The burden of autism, an incurable and serious disorder, requires consideration of all possible etiologies. In addition, the level of public concern about MMR vaccine safety is high.

Because of the limitations of the evidence, the significant public concern surrounding the issue, the risk of disease outbreaks if immunization rates fall, and the burden of autism, the committee recommends that further attention be given to this matter.

Specific recommendations regarding policy review, research and surveillance, and communication follow.

Policy Review

- The committee does not recommend a policy review at this time of the licensure of MMR vaccine or of the current schedule and recommendations for administration of MMR vaccine.

Research Regarding MMR and Autistic Spectrum Disorders

The committee concludes that further targeted research on the possible contribution of MMR vaccine to autistic spectrum disorders in some children is warranted For example:

- Use accepted case definitions and assessment protocols for autistic spectrum disorders to enhance the precision and comparability of research results.
- Explore whether exposure to MMR vaccine is a risk factor for autistic spectrum disorders in some children.

- Explore whether measles vaccine-strain virus is present in the intestines of some autistic children.
- Encourage all who submit reports to the Vaccine Adverse Event Reporting System about MMR vaccine and autism to provide as much detail and documentation as possible.

Communications

The committee heard from parents that obtaining unbiased and accurate information on the possible relationship between MMR vaccine and autistic spectrum disorder has been difficult. The Committee recommends:

- That governmental and professional organizations, CDC and the Food and Drug Administration (FDA) in particular, review some of the most prominent forms of communication regarding the relationship between MMR vaccine and autistic spectrum disorder. Direct input from parents and other stakeholders would be invaluable in conducting an evaluation of communication tools.

In its discussion of recommendations, the committee identified more general concerns that it could not adequately address in this report. It intends to address these in the future.

This concludes my oral statement. I am happy to answer any questions.

HARVARD SCHOOL
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MEDICAL SCHOOL

MARIE C. McCORMICK, MD, ScD
Sumner & Esther Feldberg Professor of
Maternal and Child Health and
Chair, Department of Maternal and Child Health

Professor of Pediatrics
Division of Newborn Medicine

May 30, 2001

Dear Ms. Birt,

I am sorry that you are so unhappy with the report; however, I think that your letter indicates several misconceptions about the process used by the committee, and the evidence available to it.

First, let me iterate that the Committee examined a broad array of epidemiological, animal model, laboratory and case report evidence. In doing so, it sought to answer two questions. Do we have any evidence that MMR causes autism? Is it possible that it does? The answer to the first question rests on the epidemiological studies. While any given study may be criticized along methodological lines, the studies available and presented to the committee encompassed a variety of designs and populations, and all consistently showed no association between MMR and autism generally, and with regressive autism in particular. It is, in my experience, unusual to see such consistency across epidemiological studies. Thus, at the population level, we could find no evidence that MMR does cause autism, and much evidence against an association.

However, we recognized that the majority of autism, 75-95%, is not regressive so that the ability of epidemiological methods to detect rare events, such as a subset of regressive autism with enteropathology due to measles-related virus might be limited. We, therefore, examined other data, including case reports, animal models and laboratory clinical information to address the question of the possibility that MMR might cause autism. In this regard, Dr. Wakefield's reports were reviewed very seriously.

Before I go through our assessment, however, I would like to step back a bit and note the criteria by which an assessment that a pathogen (virus or bacterium) causes a given condition. These criteria were initially laid out by the man who discovered the cause of TB, a disease at least as complicated as autism with varying presentations, and the development of symptoms years after exposure. The essence of the criteria is specificity; i.e. you do not see the disease without the candidate pathogen, and, if you see the pathogen, you see the disease. Over time, these have been elaborated as in the IOM reports, but the importance of specificity remains.

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The Committee had two relevant, published reports of Dr. Wakefield's experience to review. In the first, he reports on 12 individuals with a severe enteropathy, 10 of whom had regressive autism associated with MMR. However, two carried other diagnoses raising questions of the specificity of the enteropathy to autism. These concerns were further reinforced by his second report with many more individuals, some of whom had schizophrenia. The fact that these individuals also have this enteropathy again raises questions of the specificity of the relationship between measles virus and autism via this enteropathy, as schizophrenia has recently been linked to another, non-vaccine virus, herpes. Dr. Wakefield may be describing a hitherto unappreciated enteropathy in individuals with severe neurodevelopmental or neuropsychiatric syndromes, not an insignificant observation, but not one that supports the linkage between autism and MMR.

The only data on Dr. Wakefield's laboratory studies available to the Committee were that presented at our open meeting and at the Congressional hearing. Since the data are unpublished, he did not feel comfortable sharing the complete report with the Committee, because all material submitted to the Committee becomes public information. I regret as much as anyone that such presentations may be considered "prior publication" by some academic journals causing them to refuse to take certain reports, but we had to respect his request. What we did see in the presentation was internally inconsistent, as noted by Dr. Wilson. Dr. Wakefield appeared to be able to demonstrate large amounts of measles-related material using an antibody to measles but reported unable to demonstrate this material by polymerase chain reaction (PCR). Antibody tests may not be specific; antibodies will bind to substances which resemble measles but are not. In contrast, PCR is very specific. The combination suggests a non-specific reaction, a concern reinforced by some comments by Dr. Wakefield during the Congressional hearing. He seemed to indicate that the other reviewers of the report wanted evidence of strain-specific identification, and he noted that request was appropriate.

Thus, no credible evidence was presented to the Committee supporting the presence of measles vaccine-strain virus in the guts of affected children. However, even if Dr. Wakefield is successful in isolating measles from the gut, that is only the first step in demonstrating that MMR causes autism. As you heard at both meetings, the mechanism which he has postulated involving a leaky gut with toxins to the brain is implausible in view of what is known about the physiology of the gut and the physiology of the protection of the brain from blood-born threats. Other potential mechanisms could be hypothesized, but they too would still have to be proven. Finally, with this more specific information, it would have to be established what proportion of cases of autism could be attributed to this set of events. Because the information presented to the Committee was so preliminary, we felt that we could only categorize it as fragmentary. This is not a derogatory term; it is descriptive.

Now let us be very frank about the "rechallenge" data. What was presented to the Committee and at the Congressional hearing was a single slide with age along the bottom of a graph with several lines joining boxes which were described as the age at received an MMR at age four; who developed symptoms of autism, and who experienced some severe event after the second dose at age nine. We were told no details about any other of the rechallenge cases. We know nothing about their status before the vaccine; we know nothing about the type of autism, the rigor of its diagnosis or the course of the child between vaccinations; and we know nothing about the criteria by which a vaccination reaction was judged to have occurred.

This contrasts with the rechallenge case for tetanus vaccine considered strong evidence in the 1994 report by the IOM's Vaccine Safety Committee. The evidence presented to the Committee by Dr. Wakefield was far too weak to establish the case for causality from a case report. We are not concealing it; it was not submitted to the Committee, and has not, to my knowledge, been written up and submitted anywhere. The Committee's report indicates that evidence of measles vaccine-strain virus in the gut of autistic children or of regression in rechallenge case might or might not necessarily alter the causality conclusion of the committee, which is based on a body of evidence. However, the committee is interested in these types of data and calls for more research on these two points specifically.

As to the review process, you should know that the reviewers are not selected by the Committee and, until the publication of the report, are unknown to the Committee. Any reviews seen by the Committee members are anonymous (labeled A-M). The review process is managed by a review coordinator (in this case, two). The review process has two objectives: the first is to assess whether the conclusions drawn in the report are supported by the evidence in the report, and the second is assure accuracy insofar as possible. Since I did not select the reviewers, I do not know the full rationale for each one. However, I believe that the review panel selected by the Academy for this report represents an important breadth of appropriate expertise.

Contrary to your assertion, I did not provide any assurance that "no one with any ties to the vaccine manufacturers would be permitted to provide any input into this report." What I said, and what is in the report, were the criteria for selection to be on the Committee which precluded any funding (industrial or federal) for research on vaccine development or safety, personal financial holdings from vaccine manufacturers, and participation on federal and professional society vaccine advisory committees. To limit input from manufacturers, if relevant, or from researchers who have had funding from manufacturers would be as one-sided as precluding the input of the parent advocacy groups. However, no one with such ties contributed to the formulation of the conclusions and recommendations to the report, which are the responsibility of the committee only. Reviewers can never change the report; they provide comments which the committee must consider.

Whether the VAERS reports of autism flowed from the 60 Minutes segment or your own activities is a researchable question. Whatever the etiology, the Committee could not agree with you more about the need for better surveillance. There are a number of issues that will appear to pertain across the questions which we will address, and we are committed to making more definitive recommendations in the future.

As I have told you, I understand from personal and clinical experience that autism is a devastating condition. It is clearly being recognized with increasing frequency, and placing intense demands on a broad range of services. I also agree that characterizing the full range of symptoms and complications that individuals with autism experience, including the enteropathy, is an important endeavor. I am on record as arguing the same point about the follow up of very preterm infants, one of my own areas of research, in which the focus has been much too limited. The balance of autism research funding among different lines of inquiry was beyond the scope of the committee's charge, but we can all agree—as the report recommended—that additional research is needed to advance our understanding and treatment of this very terrible disease.

Sincerely,

Marie C. McCormick, MD, ScD
Professor and Chair

CC: The Honorable Tommy Thompson
Congressman Daniel Burton
Congressman David Weldon
MMC/aa

Mr. **BURTON**. Thank you, Dr. McCormick.

What does this mean? "However, the committee notes that its conclusion does not exclude the possibility that MMR vaccine could contribute to ASD in a small number of children because the epidemiological evidence lacks the precision to assess rare occurrences of a response to MMR vaccine leading to ASD and the proposed biological models linking MMR vaccine to ASD, although far from established, are nevertheless not disproved."

What does that mean?

Dr. **MCCORMICK**. What that means, I think is what Dr. Miller said, that the level of analysis you are able to do could not rule out rare occurrences.

In terms of the biological model, we were talking specifically about the type of evidence Dr. Wakefield had presented. Unfortunately, because it was an open meeting, Dr. Wakefield was reluctant to present his full range of data because it would also have to be put out on the Web and it was considered pre-published.

Mr. **BURTON**. I understand, and I do not want to cut you off, I just want to bear on this question.

On television all across the country, we saw yesterday that our health agencies and your committee said that the MMR vaccine was not going to be a contributing factor and could not cause autism.

Dr. **MCCORMICK**. Based on the evidence that we got to the committee, that is true.

Mr. **BURTON**. What does this mean, that you just said?

Dr. **MCCORMICK**. We are leaving the door open for additional evidence because we could not hear the evidence that was being presented. We were not provided the evidence on the presence of measles vaccine. It does not mean that that whole theory is going to be proven, we are just saying——

Mr. **BURTON**. Let me read this to you again, "although far from established, are nevertheless not disproved."

So what you are saying is that the causal link is not disproved. Is that right?

Dr. **MCCORMICK**. No, we are saying it is not established.

Mr. **BURTON**. But you are saying that it is not disproved.

Dr. **MCCORMICK**. It is not established, either.

Mr. **BURTON**. So you do not know, do you? Can you say categorically, 100 percent, that the MMR vaccine is not a contributing factor to autism? Can you say that?

Dr. **MCCORMICK**. No, because we said in rare cases.

Mr. **BURTON**. That is the point. You put out a report to the people of this country saying that it does not cause autism, there is no causal link, and then you have an out in the back of the thing. You cannot tell me, the committee chairman, under oath, that there is no causal link because you just do not know, do you?

Dr. **MCCORMICK**. Because in part we were not provided the evidence——

Mr. **BURTON**. Do you know?

Dr. **MCCORMICK**. I do not know.

Mr. **BURTON**. Then why did you say so in the report?

Dr. **MCCORMICK**. Because the bulk of the evidence——

Mr. BURTON. Because the bulk of the evidence? But you do not know. You just said that.

Dr. MCCORMICK. In fact, most of the reports I saw indicated that.

Mr. BURTON. Do you know what it is like to have an autistic child?

Dr. MCCORMICK. I do.

Mr. BURTON. You have an autistic child?

Dr. MCCORMICK. No. My brother has two.

Mr. BURTON. Your brother has two?

Dr. MCCORMICK. Yes.

Mr. BURTON. Then you know what he goes through?

Dr. MCCORMICK. Yes.

Mr. BURTON. Do you know how many kids are getting autism? Every 3 hours in California, there is a new child with autism. It used to be every 6 hours. You used to have 1 out of every 10,000 kids who were autistic.

We do not know all the answers. We do not know if the mercury, the thimerosal in the vaccinations are causing autism. You do not know for sure whether the MMR vaccine is causing autism.

Dr. MCCORMICK. I know it is not causing most of the cases of autism.

Mr. BURTON. But the point is, if you are the one that it does cause—if your child is the one that does get it and we find out there is a causal link, isn't that awful? Isn't that awful?

I just have to tell you, as I said to the last panel—and you heard what I said about Louis Pasteur and Dr. Barry Marshall, didn't you?

Dr. MCCORMICK. Yes.

Mr. BURTON. This is such a serious thing with hundreds of thousands of people that are going to be autistic and be a burden on society for the rest of their lives, it is going to cost us trillions of dollars—when you talk about 1 in 250 or 500 kids—they are going to grow up and they are going to be a burden on society. We should not close the door to any avenue of research to find out what is causing that.

It is not being caused just by genetics, I do not believe, because you are having a huge quantum increase in it. Something is causing it and we ought to be open to everything.

Dr. MCCORMICK. In fact, the report, sir, does recommend continued attention to this linkage.

Mr. BURTON. I know, but that is not the point.

Of course, I read that. But most people in this country did not. All they heard on television was that there is no causal link, none. I heard doctors saying that this has been studied by experts not connected to the pharmaceutical industry.

Now let me ask another question, because this is pretty important, too.

You sent this report out to a group of people to look at, didn't you?

Dr. MCCORMICK. I did not send out the report.

Mr. BURTON. Somebody sent it out, did they not?

Ms. STOIBER. I am sorry. I would answer those questions because the committee is not responsible, the Institution is.

Mr. BURTON. Stand up and be sworn.

[Witness sworn.]

Mr. BURTON. Did you send out the report to be reviewed?

Ms. STOIBER. Not personally, but institutionally, we sent out the report.

Mr. BURTON. And you sent it to Linda Cowan, Eric Fombonne, Neal Halsey, Samuel Katz, among others, right?

Ms. STOIBER. That is correct.

Mr. BURTON. Neal Halsey and Samuel Katz are people that do not subscribe to the theory that the MMR vaccine might be a contributing factor, right?

Ms. STOIBER. I have no idea, sir, what they subscribe to.

Mr. BURTON. Well, let me tell you they do. Those two people do not believe that the MMR vaccine is a contributing factor to autism.

You sent it to them for review, and I presume they went through it and might have made some modifications—I do not know—but you did not send it to Dr. Wakefield who is on the other side of the issue. Why?

Ms. STOIBER. When we select a review panel—and there are 15 reviewers to this report—we try to select people from all sides of an issue, those who believe there are connections and those who believe there may not be connections. I think in fact there are three reviewers that were specifically selected because they have the confidence and have been engaged in the research that would in fact be supported by the advocates of this connection.

We take into account all of the reviews carefully. The reviewer's comments are blinded. We do not know who they are when we receive them. And no reviewer ever has the power to change a word in our report.

Mr. BURTON. Were any of these people presenters at the conference?

Ms. STOIBER. Yes, two of the people were.

Mr. BURTON. Who were they?

Ms. STOIBER. Dr. Fombonne and Dr. Miller.

Mr. BURTON. Did Dr. Halsey or Katz, either one, present?

Ms. STOIBER. They did not.

Mr. BURTON. They did not?

Ms. STOIBER. No.

Mr. BURTON. Halsey and Katz have financial interests in pharmaceutical companies. Fombonne and Miller did present?

Ms. STOIBER. That is correct.

Mr. BURTON. And they did not agree with the thesis——

Ms. STOIBER. I am sorry. Dr. Miller did not present. It was Dr. Volkmar, Ward, and Fombonne.

Mr. BURTON. Dr. Fombonne was one of the people who reviewed it and he was a presenter on the other side of the issue, as I recall. He believed the MMR vaccine was not in any way associated with the autism.

Ms. STOIBER. He reported the results of his study, which showed no association.

Mr. BURTON. And Dr. Wakefield was on the other side of the issue. He was a presenter, as well, but he was not given a copy of this to review.

Ms. STOIBER. The reviewers, sir, were not selected because they were presenters, but were selected because they represented a wide spectrum of views on the subject. The fact that two of them also presented was totally coincidental and they were selected for their ability to provide a broad assessment of the evidence.

Again, we tried to balance, always, the reviewers selected so that those who have opposing views are equally and well represented among the reviewers.

Mr. BURTON. Do you know if any of the people that reviewed it—other than the ones I mentioned—had financial interests or connections with any pharmaceutical companies that produced the MMR vaccine?

Ms. STOIBER. To the best of our knowledge, they do not. In fact, we do not do the same kind of extensive review of the financial holdings of reviewers that we do of committee members. But to the best of our knowledge, aside from the fact that they may own mutual funds that hold pharmaceutical stocks, there is no reason to believe there are any financial ties.

Mr. BURTON. In the past, we have subpoenaed from the health agencies—and we are still going through them—the financial disclosure forms of people in the decisionmaking process who make decisions on these vaccines. So therefore I would like to know—and we would like for the Institute of Medicine to contact the people on the review committee and ask them to submit to us any holdings they have in pharmaceutical companies. If I have to, I will subpoena that.

Would you tell them? And any that are connected with an institution that gets grants from the pharmaceutical companies.

Ms. STOIBER. I will first say, sir, that they are not in a decisionmaking process.

Mr. BURTON. I understand. They were in the review process.

Ms. STOIBER. They solely reviewed. And after their reviews were received, the committee had the ability to assess whether or not to accept any of that advice. Some was accepted and some was rejected.

Mr. BURTON. When it was accepted, did it involve any changes?

Ms. STOIBER. Very few.

Mr. BURTON. Were any changes made after——

Ms. STOIBER. Always changes are made in response to review because reviewers point out weaknesses in the analysis, they point out lack of clarity in the expression, but I can say to you that no central conclusions changed during the course of review.

Mr. BURTON. We will take a look at that and I will make the decision on that after I review all this. But I want to know about the reviewers and what recommendations they made and changes. I would like to have that. I would also like to know whether or not they had any interest or got any grants of any kind from any pharmaceutical companies. I would also like to have that information from any of the people on the original report panel.

According to our request, we wanted to make sure that these people are insulted who are working on this report from any influence being exerted by any pharmaceutical company. I would like to find out if any of the people who were on that panel who wrote the report if they have any financial interest or ties and whether they got any grants from any pharmaceutical companies.

I wish you would take that request back to the agency and tell them that, if necessary, we will be glad to send them a subpoena to get this information.

Ms. STOIBER. I can assure you that no member of the committee has any financial ties to the pharmaceutical industry.

Mr. BURTON. How about grants?

Ms. STOIBER. Or grants. I do not have the authority to tell you that we can deliver the financial background of reviewers, but I will certainly take that back the Academy and assess it and get back to you.

Mr. BURTON. You can tell them that I would like to have it and if they choose not to send it, I will send them a subpoena and I will get it.

Ms. STOIBER. I think we do not have the detailed financial statements of the reviewers.

Mr. BURTON. Then how can you tell me right now that they do not have any financial interests?

Ms. STOIBER. Of the reviewers.

Mr. BURTON. How about the people on the panel?

Ms. STOIBER. For those on the panel, we have extensive financial disclosure.

Mr. BURTON. Then I want it.

Ms. STOIBER. What we do not have is the same kind of information for people who served as reviewers.

Mr. BURTON. We want that and we want to know if they got any grants of any kind from any of the pharmaceutical companies.

Dr. Weldon, sorry to take so much time.

Mr. WELDON. Mr. Chairman, I ask unanimous consent to introduce for the record a statement from the Middlebrook Family of Indialantic, FL, in my congressional district, who have struggled with autism.

Mr. BURTON. Without objection, that prepared statement will appear in the record.

[The prepared statement of Mr. and Mrs. Middlebrook follows:]

The Middlebrook Family Story

October 30th, 1998 was the darkest day of our lives. This was the day we were told that our daughter, our only child, displayed autistic tendencies. We, like most families, had never heard of autism. Later in the day, it took only half an hour of reading to realize that our daughter had autism. From this day forward our lives would be changed forever. We, as a family, were sailing into the "perfect storm".

Three months later, our daughter received her formal diagnosis. We were told that we needed to get marriage counseling, despite the fact that we had a strong marriage. We were told we needed respite care, so we could get out as a couple, once in a while. And we were told to prepare for the day that our daughter would be put in an institution.

What we were **NOT** told, was that there are effective methods for teaching autistic children including, behavioral, speech and occupational therapies. In the two and a half years since diagnosis, our daughter has developed expressive language and is able to verbally communicate her needs 100% of the time. Our daughter is toilet trained and is able to attend school with an aid. With these accomplishments alone, she has beaten the autism odds. She has beaten the odds due to the hard work and determination of a lot of people. Unfortunately, these people do not include the State, the Federal Government or our insurance company. This is only the beginning, she has a very long way to go, and she needs your help. **The message from this family is that progress can be made and autistic children can learn, when given the chance.**

Families with autistic children face daunting day-to-day challenges. In our family, we are unable to worship as a family because our daughter cannot sit in our sanctuary during services. If we chose to leave her at home, we cannot afford the additional cost of sitting services. We cannot go out to eat as a family, and indeed, there are very few places we can visit as a family outside of the home. Inside our home our daughter requires 100% supervision. Imagine having a two-year-old in a four-year-old body. My daughter can visit every room in the house in 60 seconds. Because she has no awareness of danger, simple things like roads, stoves, and swimming pools are a constant concern. Because she requires constant attention, someone has to supervise her continually. Imagine having one adult essentially unavailable to do anything but supervise a child on a continuous basis.

We are a fortunate family. Our child is not self-injurious, and does not harm others. She is toilet trained, and is able to communicate verbally. For many families this is not the case. For many, it is literally a struggle to survive. Families typically face financial ruin, and disintegration of personal relationships, including marriage, in many cases. For most it is not a question of **whether** they will go broke, but a question of **how long** it will take to get there. This is the double indignity of having a special needs child. Not only do we struggle with the situation, but we are also faced with financial ruin.

Immediately after our diagnosis I discovered in the fine print of my insurance policy, that treatment for autism was specifically excluded. It is worth noting that our child has a type of "regressive autism" that is being reported more and more often. She lost previously acquired skills. Prior to her regression, she had a vocabulary of two hundred words in both the English and Greek languages. She subsequently lost her entire vocabulary, which was reduced to ten words. She clearly is entitled to rehabilitative treatments similar to those provided to stroke victims who have lost skills. The diagnostic center, at Emory University, in Atlanta gave my daughter the dubious distinction of being "the worst case of regression they had ever seen." We have spent close to $200,000 on her therapies, and have been reimbursed for none of this. What is insurance coverage for if not to help rehabilitate our child? How can such a wealthy country, like America, not help its most needy citizens?

Many families struggle with a balancing act of caring and teaching the autistic child with the needs of the rest of the family. The remaining family members and spouse are neglected, and resources diverted to help with the expenses of autism. On top of these challenges, families are told that insurance will not cover treatment and that their child will be placed in a special education classroom. Special education classes struggle to teach these kids in an effective manner, because of the intensive one-on-one teaching methods needed. Regrettably, these options remain unavailable due to funding constraints.

These kids can learn and become productive members of society if given the chance. Some will make 100% progress, some will approach 80%, and some will reach a lower level, but **all will learn. We must allow these individuals the chance to learn and provide families with the necessary tools.**

If we do not do something as a nation now, we will have a flood of autistic individuals into the State systems in a just a few years. The well-documented increases in California are occurring in Florida and around the rest of the nation as well. Perhaps Congress should investigate exactly what the rates of incidence are in order to plan for the future.

Brad & Jenny Middlebrook

Indialantic, Florida - www.AutismInfo.com

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Mr. WELDON. Dr. McCormick, you were quoted on CNN as saying that the MMR vaccine is as safe as a vaccine can get. Is that correct?

Dr. MCCORMICK. Yes.

Mr. WELDON. If you were to find that the data, that the epidemiologic studies that have been quoted today—which I assume you reviewed and that played a key role in your decisionmaking process—correct me if I am wrong.

Dr. MCCORMICK. We were not aware of Dr. Miller's study at the time of the decision.

Mr. WELDON. How about the Taylor study?

Dr. MCCORMICK. Taylor, yes.

Mr. WELDON. If you were to find that any of that data was defective, would that affect your opinion on the safety of the MMR vaccine?

Dr. MCCORMICK. First, I think in terms of the statement that it is as safe as any vaccine can be, it is made with the understanding that all vaccines carry some degree of risk and side effects.

Mr. WELDON. Right.

Dr. MCCORMICK. We carefully looked over that epidemiologic data twice. Not only did we have a prepared review, but both Dr. Goodman and Dr. Gatsonis looked at that information again separately to look at the quality of that information.

I think any single study can be critiqued. It was the fact that there were multiple studies with different kinds of designs, looking at different populations, addressing different parts of the pie, and all the results came out the same way. It was the consistency of cross-studies that was impressive, not that any single study could not have been critiqued as not having addressed all issues.

Mr. WELDON. Were you looking at their studies or their raw data?

Dr. MCCORMICK. We were looking at the studies.

Mr. WELDON. Did you have access to the data?

Dr. MCCORMICK. No.

Mr. WELDON. The committee has asked for the data and it has not been made available to us.

Dr. MCCORMICK. We did not have the data.

Mr. WELDON. Mr. Chairman, that is the only question I have.

Mr. BURTON. Let me just ask one or two more questions.

I have here a list of the people that were on the committee. The University of Washington School of Medicine, Christopher Wilson—he is a professor there. Does the University of Washington School of Medicine get any grants from any pharmaceutical companies?

Or how about Alfred Berg, University of Washington? Or Bennet Shaywitz, Yale University? Or Gerald Medoff, professor of medicine and microbiology at Washington University School of Medicine? Or Columbia? Or Michigan? Or George Washington?

All those schools get grants from pharmaceutical companies, don't they? And don't those people who work for those universities that get those grants know those grants are paying for a lot of the research they are doing?

Ms. STOIBER. Our bias and conflict of interest excludes only the personal situation of the individual serving on the committee, their grant support or grant support in their immediate labs. Clearly, it would be very difficult to compose a committee of experts if you excluded every University in the country because they receive some grant somewhere in the university from the pharmaceutical industry.

Mr. BURTON. I understand that. But the problem is, if you are getting a large grant from a pharmaceutical company, and you know that your laboratory at whatever facility you are working at or employed by is getting that grant, and you know that they have an interest in the decision being made, don't you think that would wear a little bit on the processes on the people on the commission?

Ms. STOIBER. I genuinely do not. I think these individuals took this as the very highest level of responsibility to look at the science on its face and were not influenced by external factors of that nature. But clearly opinions could differ on that.

Mr. BURTON. Thank you.

Mr. Waxman.

Mr. WAXMAN. Dr. McCormick, a number of times during this hearing Mr. Burton has impugned the integrity of the Institute of Medicine's committee. As I understand it, the committee established strict criteria for committee membership. No one with any ties to vaccine manufacturers or their parent companies was allowed to be on the committee. No one who had ever served on a vaccine advisory committee was allowed to be on the committee. Even people who had provided expert testimony or had published about vaccine safety were excluded from the committee.

Yet the chairman insists that the report is tainted by bias. He says that after the committee wrote the report the Institute sent it out to a panel of reviewers that contained individuals with conflicts of interest and that those individuals have biased this report.

My understanding is that reputable, published scientific findings need to go through a review process. Is that correct?

Dr. MCCORMICK. I would defer to Ms. Stoiber, who has been answering these questions on institutional policy.

Ms. STOIBER. But I think he was asking about peer review generally.

Mr. WAXMAN. If you have a reputable, published scientific finding, doesn't that need to go through a review process?

Dr. MCCORMICK. Absolutely.

Mr. WAXMAN. In fact, it would have been irresponsible not to have the report reviewed. Isn't that correct?

Dr. AMARAL. I think that is one of the safeguards of the Institute of Medicine, that there is such an extensive review of reports.

Mr. WAXMAN. Was this review process any different from the process of publishing an article in a peer-reviewed journal?

Dr. MCCORMICK. It is much more extensive. It is much more critical.

Mr. WAXMAN. The chairman also continues to say that the report changed after this review process. Is this true?

Dr. MCCORMICK. There were changes of fact, there were some changes of wording to more appropriate wording. There was no change in the overarching conclusions of the report.

Mr. WAXMAN. Did the committee's recommendation change after it received the reviewer's comments?

Dr. MCCORMICK. No.

Mr. WAXMAN. If a parent came to you with concerns about the safety of the MMR vaccine, after hearing all the evidence presented to the panel and after hearing the deliberations of the panel, what advice would you give to that parent about whether to vaccinate their child?

Dr. MCCORMICK. I would give the advice that the child should be vaccinated. The risks of measles far outweigh the risks for autism. We are talking about risks of death, risks of severe chronic dementia called SSPE. These risks are real and documented as a result of wild-type virus.

I think the risks of MMR and autism should continue to be explored, but I do not think that MMR causes even the bulk of autism. The committee did not feel they had enough information themselves to make that kind of assessment, but that is my personal view. The risks of wild-type measles are real.

Mr. WAXMAN. I said in my opening statement that the committee concluded that there is "no credible scientific evidence establishing a link between the MMR vaccine and autism." Is that a correct characterization of the committee's conclusions?

Dr. MCCORMICK. Yes.

Mr. WAXMAN. In Chairman Burton's opening statement, he stated that "the committee found that there was insufficient evidence to prove conclusively or disprove a connection between the MMR vaccine and acquired autism."

That seems to me to be a gross mischaracterization of the committee's findings. The committee could have chosen to say that there was inadequate evidence, but you did not say that. You said that the evidence favors a rejection of a causal connection between the MMR vaccine and autism.

Why did the committee say that the evidence conflicts with the theory that the MMR vaccine causes autism?

Dr. MCCORMICK. The theory really has not been substantiated with a full chain of evidence. As I mentioned earlier when you were not present, Dr. Wakefield was unable to present his full data because he was reluctant to present it in a public setting before it was peer-reviewed. We left the door open that should such data come in and look more solid and that there was a causal chain we would clearly relook at the results. But it seemed to be a long way away before that kind of causal linkage was not only established but replicated in other laboratories.

Mr. WAXMAN. The Institute of Medicine report also states "its conclusion does not exclude the possibility that MMR vaccine could contribute to ASD in a small number of children."

Mr. Burton reads this and draws the conclusion that there is a lot of uncertainty about the safety of the MMR vaccine. Do you agree with this? Do you think the science raises serious questions about the safety of MMR?

Dr. MCCORMICK. No.

Mr. WAXMAN. When I read the report, I draw a different conclusion than the chairman. We all know that it is very hard to prove a negative. My understanding is that the Institute is saying that it could not prove a negative. Is that correct?

Dr. MCCORMICK. That is correct.

Mr. WAXMAN. This does not make MMR a likely cause of autism. It does not even make the MMR theory an untested hypothesis. Rather, the theory has been examined and all the epidemiological evidence points toward rejection. Is that correct?

Dr. MCCORMICK. That is correct.

Mr. WAXMAN. My time is up. Thank you, Mr. Chairman.

Mr. BURTON. But you cannot say categorically that the MMR vaccine does not cause, in any causes, autism, can you?

Dr. MCCORMICK. No, that is what the statement says.

Mr. BURTON. Thank you.

Let me just ask you two more questions.

If it is true that autistic children do not get proper medical evaluations to assess if they have gastrointestinal and immune system disregulation, as pointed out by Dr. Wakefield, how can the IOM committee conclude that the percentage of children with autism caused by MMR is small?

Dr. MCCORMICK. Because the bulk of the epidemiological evidence shows no causal connection on a population basis.

In terms of the investigations Dr. Wakefield has recommended, we, too, like Dr. Gershon, really applauded Dr. Wakefield for expanding the notions of what the problems are that these children have.

Mr. BURTON. Dr. Weldon said to the people from England, why don't you just take a look at 50 or 100 or 500 kids that have autism and gastrointestinal problems and check to see if the thesis is correct? Why not do that?

Dr. MCCORMICK. We recommended continue attention to that and for duplication of the results in the report. That was one of the recommendations.

Mr. BURTON. If that is one of the recommendations, that research is necessary, why would you put out a report that everybody in the country that was interested in this heard on television saying that there was no causal link, period. That is all we heard. I watched every channel and they all said the same thing, that there is no causal link.

Yet you just said that you cannot make a categorical statement like that.

That confuses a lot of people and it raises uncertainty even to a higher level because people want to trust the Government and this creates doubt.

I have one more question for you.

Since there has been a published report of vaccine-strain measles causing encephalitis in a healthy child, why was it stated in the IOM report that no such data existed?

Dr. MCCORMICK. We did cite it. It was found that after the primary hospitalization these children were found to have a primary immune deficiency so that they were not previously healthy children.

Mr. BURTON. Would you give me that one more time?

Dr. MCCORMICK. After hospitalization, the patient that had this measles-strain encephalitis was found to have a primary immune deficiency with a decreased CD–8 count and hypogammaglobulin. So the inflammation was thought to be due to immune deficiency.

Mr. **BURTON**. So if a child has an immune deficiency, then they are at risk for an adverse event?

Dr. **MCCORMICK**. Children with immune deficiency are at risk of a wide variety of adverse effects.

Mr. **BURTON**. From the MMR vaccine?

Dr. **MCCORMICK**. Not necessarily. It depends on the nature of the immune deficiency.

Mr. **BURTON**. Well, I want to thank you very much for being here. I do want to say, though, that because this is such an epidemic, I think our health agencies ought to look at every possible avenue, and follow every possible avenue, to find out if this is why we have this fantastic increase.

In Mr. Waxman's district in California, every 3 hours there is a new case of autism. It used to be one in every 6 hours, as you heard earlier. Nobody seems to have any idea why.

To rule out anything and then say at the end that in some cases it may not be conclusive when you do not have all the facts yet—you have not done a study on kid's guts that have autism to see if that measles vaccine is in there. It seems to me that is giving information that is not completely factual and closing a door that probably should not yet be closed.

Also, on the mercury vaccine—which you do not have anything to do with——

Dr. **MCCORMICK**. Oh, yes, we do.

Mr. **BURTON**. You will be working on the thimerosal issue?

Dr. **MCCORMICK**. That is our next report.

Mr. **BURTON**. Well, I hope you will be very, very thorough and careful when you do that report because we will have you back here again and ask you about that. It will be a very thorough hearing once again.

And I have to tell you that in our own family—and I know there are lot of people in this room who have autistic children and grandchildren—a normal child, nine shots in 1 day containing thimerosal and the MMR vaccine, and 10 days later he is gone. I just have to tell you that is really bad and we have an epidemic. We have to find the reason why.

Mr. **WAXMAN**. Mr. Chairman, my observation is this: autism is an awful disease and we have to do everything we can to fight this disease. But when we are trying to figure out how to fight a battle, you only have a certain amount of resources. If we take those resources and continue to go over and over and over a line that seems to me not very promising, we have an endless task of trying to reevaluate this theory, to try to prove whether it is a negative or a positive. It seems to me that we ought to make some decisions about whether we ought to be asking the scientists where we should put the money to fight autism.

Are we going to continue to reevaluate and have another committee reevaluate Dr. Wakefield's theory? I do not want to say that we should ignore it. I do not know the answer. I am not a scientist. I cannot give an answer. But I do not know that is the best place for money to fight autism.

And I would be interested in our committee trying to find out from scientists—I do not think scientists who disagree with Dr. Wakefield should be treated as if they are our enemy. These are people from the Institute of Medicine. They have devoted their lives to fighting disease. They are trying to fight autism.

We ought to consult with them, not challenge them. We are doing more than challenging them, we are trying to impugn their integrity because they have not come to the same conclusion as Dr. Wakefield.

We can keep putting money into Dr. Wakefield's theory over and over and over again to where we could say, maybe it is true and maybe it is not, instead of saying, maybe it is not but maybe it is.

It seems to me at some point we ought to ask what the best use of money is. Should we be looking for a vaccine for autism? Should we be looking for medicines that can cure it? Should we be doing something to help the parents? Should we be using the money for research in trying to find out the causes? Or do we know the causes?

It seems like we approach this issue as if we know the cause and there is somebody trying to keep us from keeping it open. I do not think we know the cause and I would like us not to limit ourselves in our thinking and our approach to this problem as if we know this cause and what we have is a grand conspiracy to keep this cause from being public.

I think you have done a real service, Mr. Chairman, by giving a focus on this disease and suggesting that we need to understand that this a problem that is serious and seems to be on the increase and we ought to fight it. But let us not get diverted in our fight to an endless discussion of a theory that I think is not a very promising one, from everything I have heard in the hearings, we have had—and we have had many hearings on this one theory.

So I hope we can work together to figure out some other constructive ways to fight this disease because you and others have expressed so strongly, emotionally, and well that it is our obligation to do that.

Mr. BURTON. Let me just end by saying that you have a great deal of constraints on your time, Mr. Waxman, and we have had a number of hearings. Generally, you come in and make a statement and then you leave and do not hear all the testimony and you do not have a chance to question all the witnesses.

I understand that you have these constraints on your time. I just hope that in the future when we have these hearings that you will be able to devote the time necessary to hear all the witnesses instead of just coming in and making a statement and leaving.

I do not want to cause acrimony between the two of us, but that is one of the problems. And I know you have demands on your time.

I want to say one other thing and then——

Mr. WAXMAN. I hope you will yield to me on that point.

Mr. BURTON. I will yield to you.

Mr. WAXMAN. I do have a conflict in the time because I do not get to set the agenda and we have other committees and other demands. But I do have staff. And I do have an opportunity to read the testimony. And I do have a chance to evaluate what is said. I think in doing that I have a better picture of what the different people are saying than if I sat here and heard every single person but refused to believe those that disagreed with my theory.

You can sit here for hour after hour and believe that those who say that I am right are telling the truth and those that say I am wrong are lying. That would be maybe a good use of time, but not a good use of process by which hearings ought to give us some conclusions.

Mr. BURTON. As I understand it, the way that you come to conclusions is you look at a whole body of people, and you see if there is a causal link. As I understand it, you look for the commonality of things like autism. It seems that the vast majority of the people who are becoming autistic now—the one common link is that they all suffered in relatively close proximity to these vaccines, a huge percentage of them.

So there is a commonality there. So it is logical for many people—myself included—to conclude that a lot of these autistic kids are becoming autistic because of a combination of thimerosal, the MMR vaccine—I do not know what—but that is the commonality. That is the thing we see.

And we have heard that week after week, month after month, with a whole host of people testifying from around the world. Because of that, I think we need to take a very hard look and a very thorough look at these vaccines and the contents of vaccines and whether or not maybe separate vaccines should be given.

Instead of the MMR vaccine, maybe it should be a measles shot without preservatives in it. Maybe it should be a single mumps shot. Maybe a single rubella shot. I know it would be a lot more time-consuming and more costly.

We ought to find out if we need to have mercury or thimerosal in vaccines. As I understand it, if you have single shots, you do not really need that kind of preservative in there and you can give a child a shot that does not have a possible contaminant in it.

So I hope that in your review of these vaccines containing things like thimerosal you will look very closely at that and give us a report that will be very, very thorough.

Dr. McCormick, did you have a closing comment you would like to make?

Dr. MCCORMICK. I do not think anyone sitting around our table is not concerned at our committee meetings about the safety of vaccines. That is why we are there. But also millions of children get these vaccines without developing the autistic symptoms. What we are looking at in the epidemiologic literature is the comparison of those with the vaccine and without to see to what extent we can draw the association with autism.

So that information does not support the linkage. But I do not think there is anybody sitting around our committee table that is not concerned about the safety of vaccines and is not coming to it from a neutral point of view that if they saw a risk they would not call it.

Mr. BURTON. I understand and I appreciate your comment.

But I will tell you this: it used to be 1 in 10,000 and in Indiana it is 1 in 400, and in Oregon it is 1 in 190 kids that are autistic. There has to be a cause and it appears as though one of the contributing factors are some of these vaccines.

With that, thank you very much for being here. We stand adjourned.

[Whereupon, at 3:15 p.m., the committee was adjourned to reconvene at the call of the Chair.]

[Additional information submitted for the hearing record follows:]

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U.S. House of Representatives, Committee on Government Reform
The Honorable Dan Burton, Chairman

Written Supplement to Oral Presentation
Testimony by James Jeffrey Bradstreet, M.D., F.A.A.F.P, Director of Research, IARC

April 25, 2001

I am grateful to Congressman Burton and this committee for providing me an opportunity to contribute our research and understanding of child developmental disorders for consideration in this ongoing debate over vaccine safety. I deeply respect the desire of parents, medical professionals and government agencies to limit all children's risks for serious infectious diseases. In the past several years, our research facility has treated and investigated over 1000 children with autism spectrum disorders. The vast majority of these children suffer with autoimmune and toxicological disorders, which disrupt normal immune, gastrointestinal, and neurological functions. Vaccine constituents are at least theoretically capable of inducing these changes. Mercury, Aluminum, Measles Attenuated Vaccine Strain, Pertussis Toxoid, and Hepatitis B seem to head the list of troublemakers. But vaccines are only one potential source for the rising tide of neurodevelopmentally abnormal children. Chronic exposure to environmental toxicants, particularly for the unborn, has been identified by the EPA and the WHO as serious issues. The list includes: PCBs, pesticides, complex petrochemicals, off-gases from plastics and carpets and thus the list seems to be unending for the potential problems we are creating for our children. This discussion will detail the challenges my wife and I faced in seeking care for our son, despite both being doctors (specifically, my wife is a dentist and graduated first in her class from the University of Maryland). It will also outline critical and established literature regarding mercury and vaccines, which seemingly has not been incorporated into the thought processes regarding the etiology of autism, neurodevelopmental autoimmune disorders and other childhood problems identified of late.

At a recent autism conference in Chicago, and prior to either my own presentation or that of Dr. Wakefield, I asked the audience of 500 parents if they felt their child regressed following a vaccine. In that obviously non-scientific survey, approximately 90% the parents raised their hands to affirm vaccines were what they suspected had caused their child's symptoms. When I asked for how many had reported the event under the VAERS system, fewer than 15 said they had. Then I asked if their pediatrician had offered to report this, they just laughed. I have now conducted this simple survey with over 5000 parents at conferences around the world with similar findings. Yes, media attention creates bias. But despite the informal nature of this survey, it does tell us something about this debate we are currently engaging: 1) parents of children with autism suspect vaccines damaged their child, 2) parents are not reporting this using VAERS forms, 3) pediatricians are not reporting to VAERS either, 4) and despite efforts by policymakers at CDC, FDA, AAP and elsewhere to reassure parents of the safety of vaccines, they remain unconvinced. So, do I, but for different reasons.

The data establishing thimerosal neurotoxicity from Professor Boyd Haley, Chair of the Department of Biochemistry at the University of Kentucky School of Medicine is clearly reliable. Other studies document thimerosal as both an allergen and a toxin to sodium channels. The lack of safety trials on vaccine schedules (not merely a single vaccine) in significantly large enough populations of children is completely lacking. Interference of measles virus and other live viruses has been established, and therefore causes great concern. Measles vaccine virus genome has been recovered from the brain of one previously healthy child in Canada over eight months following vaccination, thereby substantiating prolonged latency concerns. A recent Mayo Clinic study adds weight to the measles/inflammatory bowel disease arguments. Measles viruses cause endothelial damage to blood vessels and trigger the type of autoimmunity we observe in our patient populations. We are unusual in the world in that we vaccinate babies to hepatitis B virus. This vaccine is well known to trigger autoimmune and neurological reactions, while the disease it is supposed to prevent is almost exclusively spread through sharing needles and high-risk sexual activities. Obviously, the vast majority of children are at no risk for this disorder in the US. Aluminum, an adjunct in the vaccines is added to stimulate excessive TH-2 immune responses. TH-2 over-weighting is associated with allergies and autoimmunity. Both of these disorders are on the rise in the general population and our children as well. Finally, the intramuscular mode of administration is wholly different from usual exposure to the diseases the vaccines are supposed to prevent. This route by injection, as opposed to nasal or pharyngeal exposure, may in itself be problematic, since it bypasses much of the natural immune system present in the upper respiratory tract, where it might be more appropriately managed.

If my wife and I as parents and health care professionals faced daunting and complex decisions, with far less medical data and resources than we would have hoped for, how much more complex is this for parents with less education and more modest incomes? The answer to that question came from one parent who recently told me, "I feel like that warning you get on airplanes, *in the event of an emergency please place the oxygen mask on yourself before helping small children*." Even as a physician, I was overwhelmed and unprepared for what lay before me, and so are all parents facing vaccine-precipitated problems. But so are most of the professionals parents need to trust to take care of these problems.

My son's pediatrician once told me that just because Matthew hid under his exam table spinning the wheels of a toy truck over and over again, or had no eye contact, or couldn't perform any motor skills typical of his age, or talk in a meaningful way – well none of that meant he was anything but a late bloomer. After all, he did have an older sister who was more than willing to talk for him. That profound lack of understanding for

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developmental disorders seems surprisingly common. Most parents tell me similar stories.

However, the lack of local support proved to be a blessing, since it forced me to become educated. I took to the web, made phone calls to experts, went to the medical school library, and then started taking my son to any physician who might be able to help. My search took me to NICMH/NIH and even to Europe twice. It has been an evolutionary process for my understanding of this very complex disorder mislabeled – autism. I will speak to this later, but autism is a term for a collection of symptoms created by psychologists and psychiatrists, with no knowledge of the biomedical abnormalities present in the children. No fault to them, but we do know better now, as this exploration of the medical literature will substantiate.

My Son's Journey

My interest in this field of research and treatment went from zero in 1994, when my son Matthew was born, to 100% of my efforts by 1998, when local efforts to help my son's autism proved unsuccessful. Matthew was a happy, normally developing child until a few weeks following his 15 month MMR, HIB and Varivax injections. By eighteen months, he was obsessed with spinning tires on toy trucks and would not respond to his name. Neither did he respond to pain in any way. A normal fall on the driveway, which should cause a typical child to go crying to mommy, didn't seem to be noticed by Matthew. He also developed chronic diarrhea, which persisted until his first infusion of Secretin in Baltimore Maryland. He went from sleeping through the night to screaming and tantruming often without rest for any of us. Then he developed explosive diarrhea.

Evaluations of his brain autoantibodies by Dr. Singh, then at the University of Michigan, revealed high levels of reactivity to his myelin basic protein, neuronal filament protein and to measles virus. Myelin Basic Protein serves as the key insulator of the central nervous system, and neuronal filament protein provides the structural support for nerve fibers. These critical structures of his brain had become the enemy of his immune system. After consultation with immunologists at several medical schools, Matthew began a course of high-dose human immunoglobulin therapy every 4 weeks. This was not compensated for by his insurance plan, because it was felt to be experimental. The annual cost of Matthew's medical, behavioral and other therapies exceeds $50,000. Less than $5,000 is covered by insurance. Because of intensive biomedical and behavioral therapies, Matthew now has recovered much of what he lost. Despite what now appears to be overwhelming evidence of an association between Matthew's autoimmunity and the MMR vaccine and mercury exposure, his mother and I have purposefully refrained from filing an action for damages under vaccine injury compensation fund, so that our desire to help other children might be clearly seen.

As a physician, I was also allowed to attend Matthew's upper and lower endoscopy whe his chronic GI problems took us to Royal Free Hospital in London. I reviewed the biopsies with the pathologists and gastroenterologists. I saw for myself the inflammatory changes, which for years had resulted in severe intermittent diarrhea and abdominal pain for my son. Unfortunately, the final TaqMan PCR studies are yet to be completed at the time of this writing.

The Need To Know Causality

My quest since has been to find out why this happened, in the hope that understanding causation would aid therapeutic interventions. I am a father, a physician and a clinical researcher. My involvement in viral research dates back to the mid-70's when I worked with Dr. Lancz, in the medical virology research lab at the University of South Florida College of Medicine. I contributed to the first NICMH, summit on the use of secretin in autism. I have presented papers and lectures at conferences all over the world. Our patients come from every continent and every race is affected. I am not in the blame business. I am in the business of helping biologically wounded children.

> The recent Surgeon General report on child mental health provides us this comment.
>
> ***"The burden of suffering experienced by children with mental health needs and their families has created a health crisis in this country. Growing numbers of children are suffering needlessly because their emotional, behavioral, and developmental needs are not being met by those very institutions, which were explicitly created to take care of them. It is time that we as a Nation took seriously the task of preventing mental health problems and treating mental illnesses in youth."***
>
> (http://www.surgeongeneral.gov/cmh/childreport.htm)

My firsthand experience forces me to agree, and I'm sure you will as well. So, regardless of your opinion regarding vaccines, or even the ultimate truth regarding vaccine safety or the lack thereof, we are at a crossroads. The neurological health of this and subsequent generations of children is at stake. **An international neurodevelopmental crisis exists, and we either deal with it effectively or loose at least one in ten children to developmental disasters like autism**. It is no longer just the government's problem. It is no longer just the one in ten families' problem. It is a problem that threatens to unravel the fabric of our society, since every nation requires sound-minded citizens and leadership. I therefore advocate government – private partnerships aimed at both finding the causes of this disaster and to provide for the needs of the children and families immediately affected by this.

Personal And Societal Costs

With autism, the lifetime costs considering the lost wages and costs of caring for a child who will eventually grow up to be an adult, may readily exceed $3 million dollars. This figure can be estimated from average wages lost and typical cost of assisted living and

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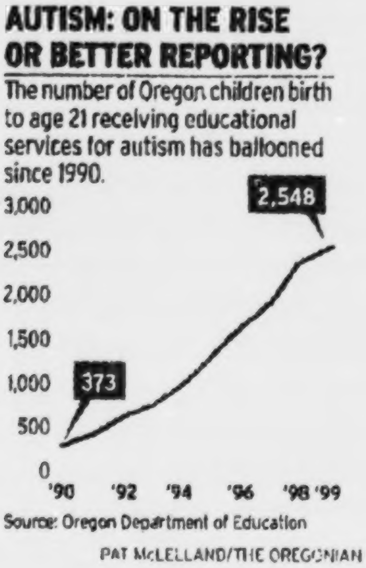
therapies. If we use average wages of $20,000/year over a 45 year career that would equal $900,000. Typical annual group home fees or behavioral therapy programs cost $35,000 (in 2001 dollars) from age 2 to age 75 would cost over $2.5 million. Combining these totals over $3.4 million. Unfortunately, we now are looking at a disorder, which has increased at least SEVEN fold in the past decade. There is no evidence of a plateau in this rise either. The families impacted by this tragedy cannot possibly bare all these costs themselves. We, as a society, have a responsibility to help those individuals who sacrificed their health for the implied greater good of public health, and to stop the assault on this generation of children.

Occurrence and Incidence Findings



AUTISM: ON THE RISE OR BETTER REPORTING?

The number of Oregon children birth to age 21 receiving educational services for autism has ballooned since 1990.

Source: Oregon Department of Education

PAT McLELLAND/THE OREGONIAN

Graphic from *The Orgeonian* – Nov 2000. Based on information available from the State of Oregon (http://www.ode.state.or.us/) the actual incidence is a little more than ½ of one percent or about 1/190 students in that state (by 2001, just over 3000 students with autism of a total of 567,000 enrolled students). This does not take into account preschoolers. Oregon, as of July 2000, has 3,436,750 residents (http://www.upa.pdx.edu/CPRC/). That makes autism in the school-aged population just under 1/10th of one percent of the Oregon population as a whole. The United States has as of the 2000 census

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281,400,000 people, 60,000 are under the age of 15. (http://www.census.gov/population/cen2000/c2kbr01-2.pdf).

At a rate of 1:190 students, that yields approximately 316,000 children (age 14 or younger) with strictly defined autism in the U.S. today. We get similar numbers if we apply the nearly 1/10th of one percent figure to the entire U.S. population. The number for the entire U.S. at that rate is 281,000. If the rate were 1:10,000 as some have suggested the number would be only 6,000 children under age 15, which would mean half live in Oregon and about 1/6th were under my care. It is time to come to terms with reality. Autism may have been a rare disease 10 years ago, but it is now extremely common.

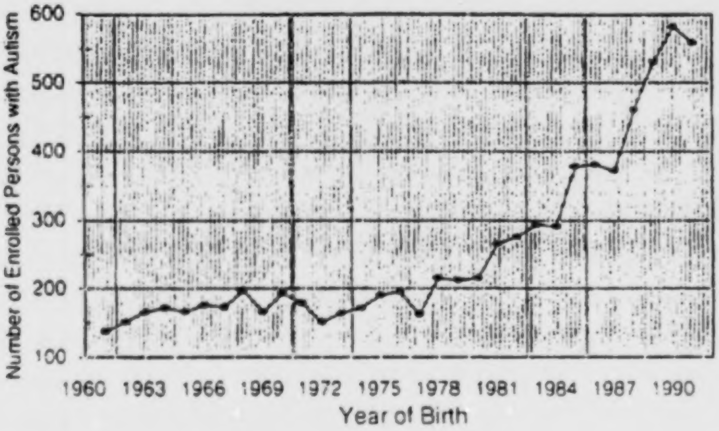
Is Oregon unique? No. Numerous states and individual school districts have reported very similar stats. So, Brick Township, New Jersey and Granite Bay, California, or Palm Bay, Florida, are not isolated pockets of autism. They are merely reporting the national trend.

By further checking with the Florida Department of Education (http://www.firn.edu/doe/doehome.htm) one can easily search the individual public and charter school database (http://info.doe.state.fl.us/fsir/indicators.cfm), and find most Florida schools indicate 10 –25% of their students are disabled. The exact nature of the disability is difficult to determine, but what an appalling statistic (1:10 to 1:4) DISABLED.

At this point, can anyone really claim this is merely better reporting than in 1990? Doctors may blow the diagnosis of autism, but no teacher misses it by first grade. Autism is a severe developmental delay, which cannot be ignored or overlooked, unlike the speculation of some critics regarding ADHD. Autism is so profoundly worse than ADHD it is specious to conclude this is a better reporting phenomena. A minimum of one tenth of one percent of the entire US population has autism and that is a disaster with massive impact on our country.

Supporting Evidence Comes from Many Sources (examples):

Figure 1 - Distribution of Birth Dates of Regional Center Eligible Persons with Autism



Source: State of California

Source ***British Medical Journal, Feb 2001***

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By referencing the Americans with Disability: 1997 – Table 5 U.S. Census Bureau data we find the following data: source http://www.census.gov/hhes/www/disability.html

Children known to have developmental delay or disability (a common synonym for autism related disorders – a broader category than strict autism, but potentially casually related)

Ages 0-2	206,000
Ages 3-5	335,000
Ages 6-14	1,611,000
Total	**2,152,000**

(Children under the age of 15)

Children ages 6-14 with possibly related conditions

Difficulty doing schoolwork	2,446,000
Socially Impaired	647,000
Learning Disabled	1,867,000
Total	**4,960,000**

So, by the government's data as many as 7 million children have a significant developmental disorder and over 2 million have a developmental delay which may be of the autism spectrum of disorders.

It is important to note here that the data from the thimerosal literature indicates subtle neurodevelopmental injury from this compound alone. (see references in the thimerosal section). Nearly all children in the U.S. have been exposed to thimerosal and we must ask how many of these disorders are the subtle effects of mercury intoxication?

Several comments are necessary regarding these data.

1) Whether MMR vaccine rates remained constant during this period does not mean MMR has no causal role in autism autoimmune symptoms or the rising incidence of autism, since the viruses may be reacting to other triggers and interfering substances, which have been added. Several additional vaccines have come on line during this time frame and these may be interacting with MMR.
2) We know autism used to rare but that is suddenly no longer the case. Subtly brain injured children now seem to comprise 1:10 students and 1:190 have autism.
3) A new variable has been added to cause this problem, since a genetic model cannot explain the sudden rise.
4) The vaccine issue is a likely place to look given the biological behavior of the vaccine components.
5) Hepatitis B, Hemophilus Influenza B (HIB) and other vaccines are capable of anti-brain autoimmunity as well. Whether these may be interacting with MMR is unknown, and therefore cannot be excluded.

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6) None of these epidemiological studies take the cumulative total dose of thimerosal into consideration.
7) The Department of Education Stats (as impressive as they are) are missing a significant number of home-schooled children with autism. My own son is an example of this. He has a fulltime ABA therapist educating him in a private one-on-one classroom setting coordinated by Professors at Florida Institute of Technology. All of this takes place outside of the normal education channels in a registered home-school setting.
8) Irrespective of causality something extrinsic has influenced the health of this generation of children, and our society will not survive this dramatic generational trend in declining mental health. Immediate action aimed at determining causation and remedy is required. This will demand an open-minded, creative and objective assessment of possible issues. It also requires an immediate risk reduction in all variables, which may contribute - even in small ways to childhood mental health disorders.

Recommendations For Immediate Action

We, as a society, must take responsibility for this disaster and do what we can to help while simultaneously finding the source of the problem so corrective steps can be made. In this light I would advocate the following:

1. Creation of a website to coordinate private organizational efforts at research and therapy. This website could cost-effectively direct interested person to grant monies and collaborations with other agencies.
2. Take legislative initiative to mandate insurance carriers provide medical benefits for the medical diagnosis and treatment of autism spectrum disorders, including PDD-NOS and Childhood Disintegration Disorder (ERISA providers).
3. Promulgate Federal Guidelines for the implementation of new Medicaid guidelines and the expansion of Medicaid waiver programs to include children affected with neurodevelopmental disorders.
4. Private and public granting of research, since university professors have expressed the fear of being blacklisted by pharmaceutical companies for research into adverse vaccine events.
5. Consideration for no-fault legislation for vaccine manufacturers, to remove the fear of catastrophic losses from the brewing class-action lawsuits. To this end, amending the present law by including the thimerosal toxicology issues in the vaccine compensation fund would be wise.
6. Raising the contribution to the vaccine injury fund to meet the projected increased filings presently within the system and those additional cases, which will arise as this becomes more public.
7. Either using the vaccine injury fund with appropriate increased assessments, or a separate vaccine cost assessment to fund research into vaccine injury and treatment.
8. Restructuring the vaccine compensation table to include current understanding of delayed onset live viral vaccine reactions. This was well documented in the following article: **Measles inclusion-body encephalitis caused by the vaccine**

strain of measles virus. Bitnun A, etal, ***Clin Infect Dis*** **1999 Oct;29(4):855-61** Department of Critical Care Medicine, The Hospital for Sick Children, Toronto, Ontario, Canada. Abstract: "**We report a case of measles inclusion-body encephalitis (MIBE) occurring in an apparently healthy 21-month-old boy 8.5 months after measles-mumps-rubella vaccination.** He had no prior evidence of immune deficiency and no history of measles exposure or clinical disease. The presence of measles virus in the brain tissue was confirmed by reverse transcription polymerase chain reaction. The nucleotide sequence in the nucleoprotein and fusion gene regions was **identical to that of the Moraten and Schwarz vaccine strains**; the fusion gene differed from known genotype A wild-type viruses."

9. Therefore, extension of the statute of limitations for vaccine related neurodevelopmental disorders, and creation of guidelines, which take into consideration the autoimmune-delayed infection aspects of this condition. This is necessary because of widespread lack of understanding of this disorder by clinicians and hence under-reporting of vaccine reactions. It is also necessary to provide public assistance for children harmed in this way.
10. The decline in public confidence regarding vaccine safety is the offshoot of recent failures. The post-release withdrawal of rotovirus vaccine, followed by the confusion regarding the hepatitis B/thimerosal issues, the MMR controversy, and the withdrawal of oral polio, have effectively communicated to the public that policy makers do not have all the answers, nor do they require adequate safety information prior to release of vaccines. Creation of a parent/professional panel to address the public's concerns with current vaccine policies might help. The rate of religious exemptions for vaccines is at an all time high. Parents are home-schooling children to prevent vaccination, and the anti-vaccine internet traffic is up dramatically. Certainly parents have the right to opt out of vaccination, and even the CDC concedes vaccination is voluntary. We are, however, in the midst of throwing the baby out with the bath water. Optional vaccine schedules could be created which allow for separated MMR components, delayed or optional hepatitis B vaccine, mandatory vitamin A supplementation prior to measles vaccine, and such.
11. Improvement of medical school, pediatric and family practice residency programs to include curricula addressing neurodevelopmental disorders, autism, vaccine reactions, and the proper use of the VAERS system.
12. Provide every parent a VAERS form at the time of vaccination and a list of symptoms, which may be vaccine related. This would allow for a more accurate parent-dependant response.

Autism or Autoimmune Post-Vaccinal Encephalopathy and Enterocolitis? Starting With The Right Diagnosis.

It is now apparent in our patient population that approximately 85% of the children labeled autistic, in fact have an autoimmune disorder usually targeting brain proteins. Additionally, they have evidence of autoimmunity to their gastrointestinal system as well.

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I believe the more medically appropriate diagnoses are: 1) post-vaccinal autoimmune encephalopathy due to a combined effect of mercury, measles/mumps interactions, and other vaccine components, 2) immune dysregulation likely due to aluminum, mercury, measles, and other vaccine components, and 3) a new unique autoimmune inflammatory bowel disease presently termed autistic enterocolitis or LNH, again presumably from the previously mentioned factors. These are now well documented in the medical literature.

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Intrinsic Versus Extrinsic Factors

Over the past decade, the majority of federal dollars for autism research have been channeled into genetics research. It is now apparent that genetics (an intrinsic factor) alone cannot explain the observed increased incidence of autism. At the very least extrinsic variables including: environmental, infectious, immunological or toxicological insult must be presumed as triggering events. Individual susceptibility to these triggers may include genetic variables, and it would be terrific to know what those genetic markers include. But our immediate responsibility is to reduce exposure to those extrinsic factors. We can start the process with a series of questions. Is thimerosal an extrinsic toxin? Yes. Can it cause some or most of the observed deficits in children with developmental delays? Yes. Can Measles in conjunction with Mumps increase the likelihood of autoimmune reactions? Yes. Do Measles and Mumps, by necessity of public health, have to be given at the same time? No. Continuing this form of logical analysis of the facts can help us to reduce the exposure to potential extrinsic triggers. This is especially important because we cannot identify whom those children are who are at risk.

A Crisis In Public Confidence

Historically, I believe vaccines appear to deserve credit for great success in reducing epidemics such as polio, smallpox and measles. But there has never been justification for placing a serious toxin, like thimerosal, into a product designed to be injected into babies. Single dose vials as used in Europe need no thimerosal. This error alone brings into doubt the public's confidence in our entire effort to prevent serious diseases. I am a Fellow of the American Academy of Family Practitioners, an organization, which works closely with the CDC and the American Academy of Pediatrics in developing the current vaccine schedule. I am not in anyway suggesting an anti-vaccine approach.

I am, however, strongly of the belief that a great deal of additional research beyond what has been accomplished to date, would have been required to understand the safety and appropriate timing for the presently available vaccines. For example, does the risk/benefit calculation for hepatitis B vaccine make sense for a five-minute old child? And if hepatitis vaccine were to cause neurological problems in that child, how would we know it was the vaccine and not some congenital syndrome? This is therefore, just one of the many reasons for marked under-reporting of vaccine injuries. And despite the fact that 50% of the parents who come to see me believe vaccines caused their children's neurodevelopmental disorders, fewer than 5% have ever reported it with a VAERS form at the time of their visit to our clinic. Further, despite the fact parents notice children declined markedly within days of the MMR vaccine, some to the point of hospitalization, no primary care physician has ever been observed in our patient population to initiate a VAERS filing. Therefore, we must assume a belief in the safety of vaccines based on the VAERS system is unwise at best. Dr. Bonnie Dunbar, the Director of Cell Biology at Baylor College of Medicine, echoed this during the 1999 Congressional hearings on hepatitis vaccine safety.

The Need For An Individualized Approach

In preparing this discussion of vaccinations and their possible role in the causation of childhood developmental disorders, it became clear that our current vaccination schedules lack consideration for individual needs and risks assessments. By individual needs and risks I mean:

1. A consideration for that child's environment – crowded inner city housing projects where disease may be rapidly transmitted, as opposed to remote farming communities or suburbia.
2. A consideration for that child's health and genetics – as in concurrent infections, prematurity, family history of vaccine reactions, or family history of autoimmune diseases.
3. A consideration for that child's sociological setting – as in how likely is the family to obtain medical care for acute illnesses, to comply with medical advice or follow treatment schedules.
4. Consideration for that child's nutritional status – evaluation for zinc or vitamin A deficiency prior to vaccination to mention a few critical issues.
5. A consideration for that child's total risk of exposure to mercury from perinatal sources – RhoGam®, mother's fish intake, mother's profession (dentistry related exposure), mother's amalgam surface area and finally mother's thimerosal exposure from recent vaccinations given prior to pregnancy or while breast feeding – when considering that child's postnatal mercury risk from thimerosal containing vaccines.
6. And lastly, an apparent widespread lack of physician experience and training in recognizing potential vaccine reactions, such as post-vaccinal encephalopathy or subtle mercury toxicity. This provides additional problems with vaccine complication reporting.

For this latter item, if current data were to be believed, MMR reactions by example occur in less than 1 of every 10,000 doses given. That makes it a very low priority in residency training programs. But new evidence suggests the present combined risks from multiple vaccine reactions of all types may be much greater than previously suspected. The complexity of multivariate analyses make this possibility an epidemiological nightmare.

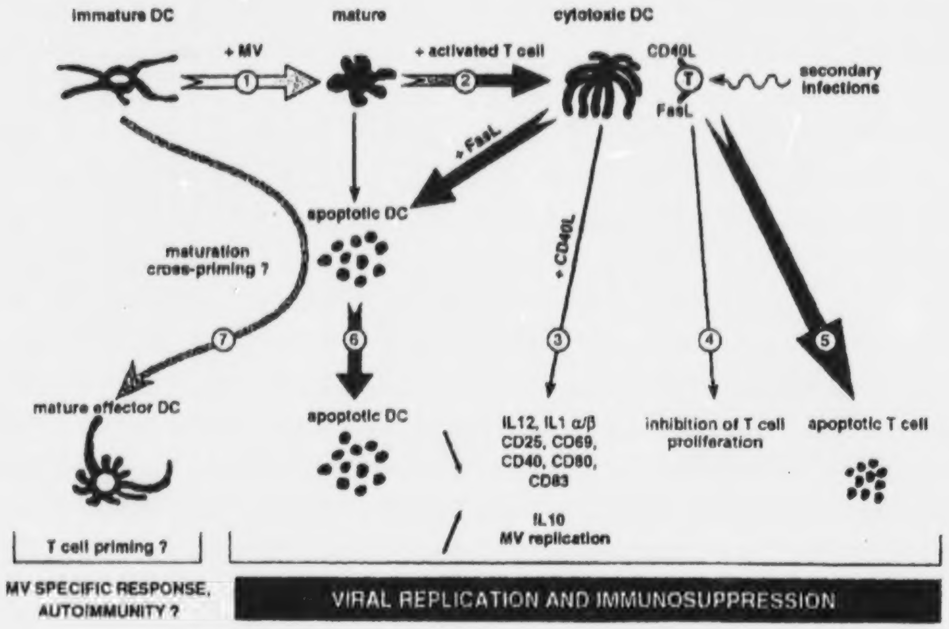
Unfortunately, when a parent brings me a child who has developed a slow progressive encephalopathy shortly after combined MMR, Hemophilus Influenza B, DaPT, Hepatitis B and Varicella vaccines, I have no data from medical safety studies to tell me if this combination was safe. I can find relatively small individual studies on single vaccines and occasional studies on two vaccine combinations. But there is a complete lack safety studies on these more complicated vaccine schedules.

We know that numerous immunological disorders are on the rise. The incidence of asthma related deaths have increased in every decade for 40 years. We know from several credible sources that the incidence of autism likely has increased as much as 7 fold in the past decade. Autism is a disorder with well-documented autoimmune and immunological disturbances. Attention Deficit Hyperactivity Disorder may affect 1 in 10 school-age children, and also has documented allergic and immunological features. We also know vaccine constituents including genetically altered protein components, live viruses, aluminum, and mercury to name a few, are more than capable of creating immunological and autoimmune disorders. Therefore, we face at least the theoretical risk that vaccines are behind some proportion of these dramatically increasing serious disorders.

Measles Virus as a Potent Immune Suppressor and Autoimmune Inducer.

Perhaps the most serious problem encountered with the MMR vaccine comes from a general lack of awareness by most physicians and many policy makers regarding the true nature of measles viral infection or measles and mumps co-infections. Measles is now well documented as an immune disruptor. The process of attenuation does not preclude it from this same process. See the section on Measles and Immune Suppression. The following graphic illustrates this problem from the brain's perspective.

SPECIAL GRAPHIC FROM RECENT REVIEW ARTICLE


immature DC
mature
cytotoxic DC
+ MV
①
+ activated T cell
②
CD40L
T
FasL
secondary infections
+ FasL
apoptotic DC
maturation cross-priming ?
+ CD40L
⑦
⑥
③
④
⑤
mature effector DC
apoptotic DC
IL12, IL1 α/β CD25, CD69, CD40, CD80, CD83
IL10 MV replication
inhibition of T cell proliferation
apoptotic T cell
T cell priming ?
MV SPECIFIC RESPONSE, AUTOIMMUNITY ?
VIRAL REPLICATION AND IMMUNOSUPPRESSION

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From: Journal of Virology, May 2000, p. 4387-4393, Vol. 74, No. 9.
This chart depicts the mechanisms by which measles virus (MV) infects certain cells and then programs either cell death in the brain or autoimmunity to the brain.

A Hard Look At The Abnormalities Facing Children With Autism and/or Post-Vaccinal Encephalopathy.

One of the core medical textbooks in this area is *Developmental-Behavioral Pediatrics*, Levine, Carey and Crocker, 3rd Edition, 1999. On page 598 the authors state with respect to the diagnostic laboratory test required in autism, "Similarly, no "routine" laboratory tests seem necessary, but close attention to possible genetic or metabolic indicators should guide the clinician's actions." It should come as no surprise therefore, that most pediatricians, developmental pediatricians, or neurologists are completely unaware of biological markers present in most children with autism. As mentioned above, the majority of children with this syndrome have autoimmunity to one or more critical brain proteins. They have marked abnormalities of their immune system. They have evidence of mercury and or lead overload. They have disorders of their coagulation pathways.

Cases Studies From the International Autism Research Center - Florida

The following are examples of commonly observed abnormal studies from children treated at the IARC. All results used with permission of the parents. The examples document the diagnostic and therapeutic challenges facing clinicians once they start scratching the surface and looking at the underlying pathophysiology. Once, I as a physician, have this data, I must react to it in some way. It cannot be ignored.

Anti-Myelin Basic Protein Autoantibodies in a 3 y.o. boy with post-vaccinal encephalopathy :

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SPECIALTY LABORATORIES
2211 Michigan Avenue 310·828·6543
Santa Monica, CA 90404-3900 800·421·4449

42500	098-3362950
COLTON	
BRADSTREET, J.J.	
	01/13/00 02 00
01/15/00 04:09	01/25/00 16 09

FINAL

DR J BRADSTREET
1663 GEORGIA ST #700

PALM BAY FL 32907

AGE: 3 Y SEX: Male

	RESULT		REFERENCE RANGE
MYELIN BASIC PROTEIN (MBP) AUTOANTIBODIES			
MBP Autoabs	46	H	EIA Units (< 10)

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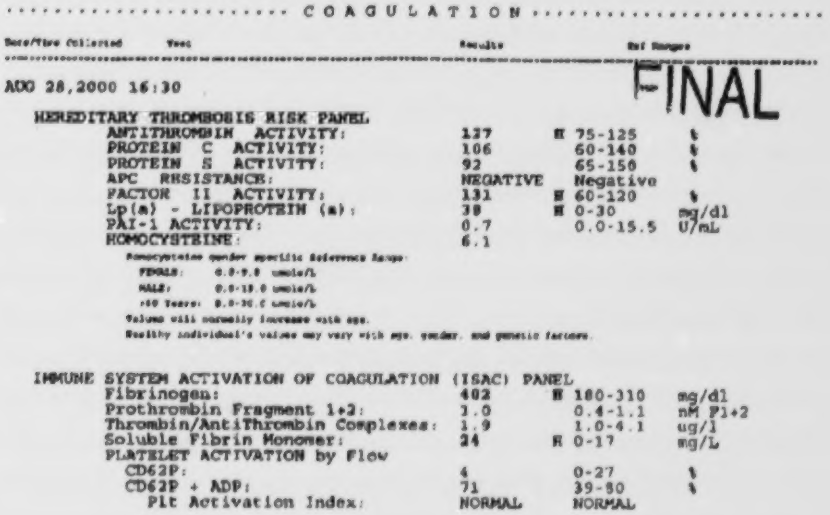
Coagulation Disorder in 7 y.o. girl with post-vaccinal encephalopathy:



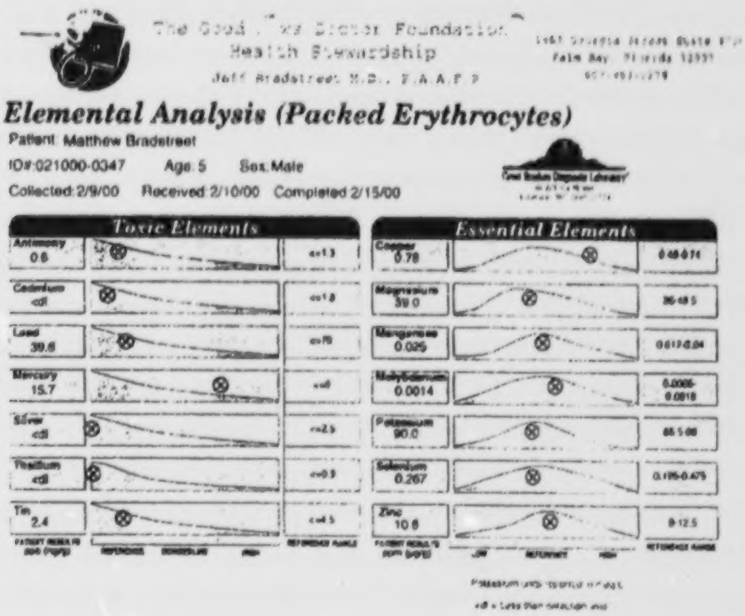
```
························ C O A G U L A T I O N ························

Date/Time Collected    Test                                  Results        Ref Ranges
------------------------------------------------------------------------------------------
AUG 28,2000 16:30                                                              FINAL

   HEREDITARY THROMBOSIS RISK PANEL
           ANTITHROMBIN  ACTIVITY:                          127        H 75-125     %
           PROTEIN  C  ACTIVITY:                            106          60-140     %
           PROTEIN  S  ACTIVITY:                            92           65-150     %
           APC  RESISTANCE:                                 NEGATIVE     Negative
           FACTOR  II  ACTIVITY:                            131        H 60-120     %
           Lp(a) - LIPOPROTEIN (a):                         38         H 0-30       mg/dl
           PAI-1 ACTIVITY:                                  0.7          0.0-15.5   U/mL
           HOMOCYSTEINE:                                    6.1
             Homocysteine gender specific Reference Range:
               FEMALE:    0.0-9.0  umole/L
               MALE:      0.0-13.0 umole/L
               >60 Years: 0.0-20.0 umole/L
             Values will normally increase with age.
             Healthy individual's values may vary with age, gender, and genetic factors.

   IMMUNE SYSTEM ACTIVATION OF COAGULATION (ISAC) PANEL
           Fibrinogen:                                      402        H 180-310    mg/dl
           Prothrombin Fragment 1+2:                        1.0          0.4-1.1    nM F1+2
           Thrombin/AntiThrombin Complexes:                 1.9          1.0-4.1    ug/l
           Soluble Fibrin Monomer:                          24         H 0-17       mg/L
           PLATELET ACTIVATION by Flow
             CD62P:                                         4            0-27       %
             CD62P + ADP:                                   71           39-80      %
               Plt Activation Index:                        NORMAL       NORMAL
```

Mercury in Packed Erythrocytes Following the Full Course of Vaccines – Matthew Bradstreet (author's child), anti-MBP and anti-NaFP also Positive:



The Good News Doctor Foundation
Health Stewardship
Jeff Bradstreet M.D., F.A.A.F.P

Elemental Analysis (Packed Erythrocytes)

Patient: Matthew Bradstreet
ID#:021000-0347 Age: 5 Sex: Male
Collected: 2/9/00 Received: 2/10/00 Completed: 2/15/00

Toxic Elements	Patient Result	Reference Range
Antimony	0.6	<=1.3
Cadmium	<dl	<=1.8
Lead	39.6	<=70
Mercury	15.7	<=8
Silver	<dl	<=2.5
Thallium	<dl	<=0.3
Tin	2.4	<=4.5

Essential Elements	Patient Result	Reference Range
Copper	0.70	0.48-0.74
Magnesium	39.0	36-48.5
Manganese	0.025	0.017-0.04
Molybdenum	0.0014	0.0005-0.0018
Potassium	90.0	85-108
Selenium	0.267	0.195-0.475
Zinc	10.6	9-12.5

Potassium units reported in mg/L
<dl = Less than detection limit

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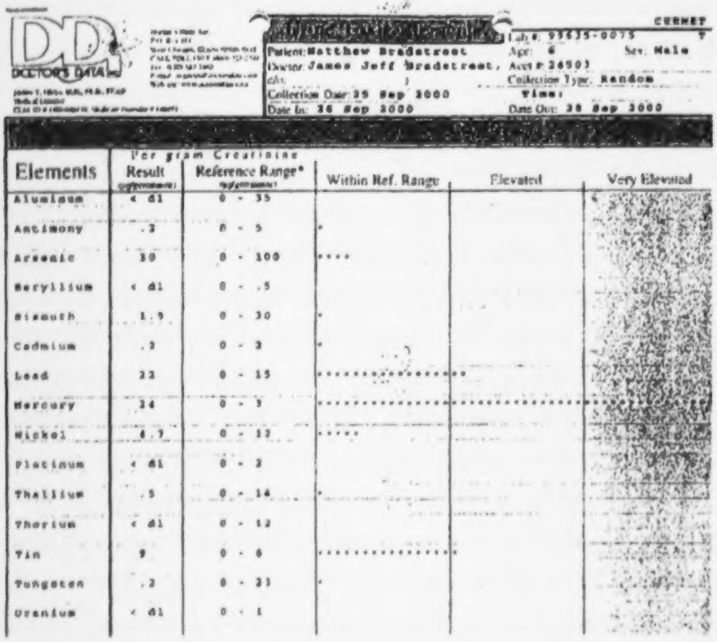
Mercury in Urine following DMSA prevocational challenge in my child:



CURRENT

Patient: Matthew Bradstreet	Lab #: 93635-0075
Doctor: James Jeff Bradstreet,	Age: 6 Sex: Male
c/o:	Acct # 24503
	Collection Type: Random
Collection Date: 25 Sep 2000	Time:
Date In: 26 Sep 2000	Date Out: 28 Sep 2000

Elements	Per gram Creatinine Result	 Reference Range*	Within Ref. Range	Elevated	Very Elevated
Aluminum	< dl	0 - 35			
Antimony	.3	0 - 5	•		
Arsenic	30	0 - 100	••••		
Beryllium	< dl	0 - .5			
Bismuth	1.9	0 - 30	•		
Cadmium	.3	0 - 2	•		
Lead	22	0 - 15	••••••••••••••••	••	
Mercury	24	0 - 3	••••••••••••••••	••••••••••••••••	••••••••
Nickel	4.7	0 - 12	•••••		
Platinum	< dl	0 - 2			
Thallium	.5	0 - 14	•		
Thorium	< dl	0 - 12			
Tin	9	0 - 6	•••••••••••••••	•	
Tungsten	.2	0 - 23	•		
Uranium	< dl	0 - 1			

The next series of four lab data represent the finding of commonly elevated copper and decreased erythrocyte zinc level. Zinc deficiency predisposes to mercury toxicity. Copper is a co-toxin with mercury in the brain, so this pattern may represent the vulnerability to mercury or derangement of normal metal metabolism. Several show marked increase in toxic minerals especially MERCURY.

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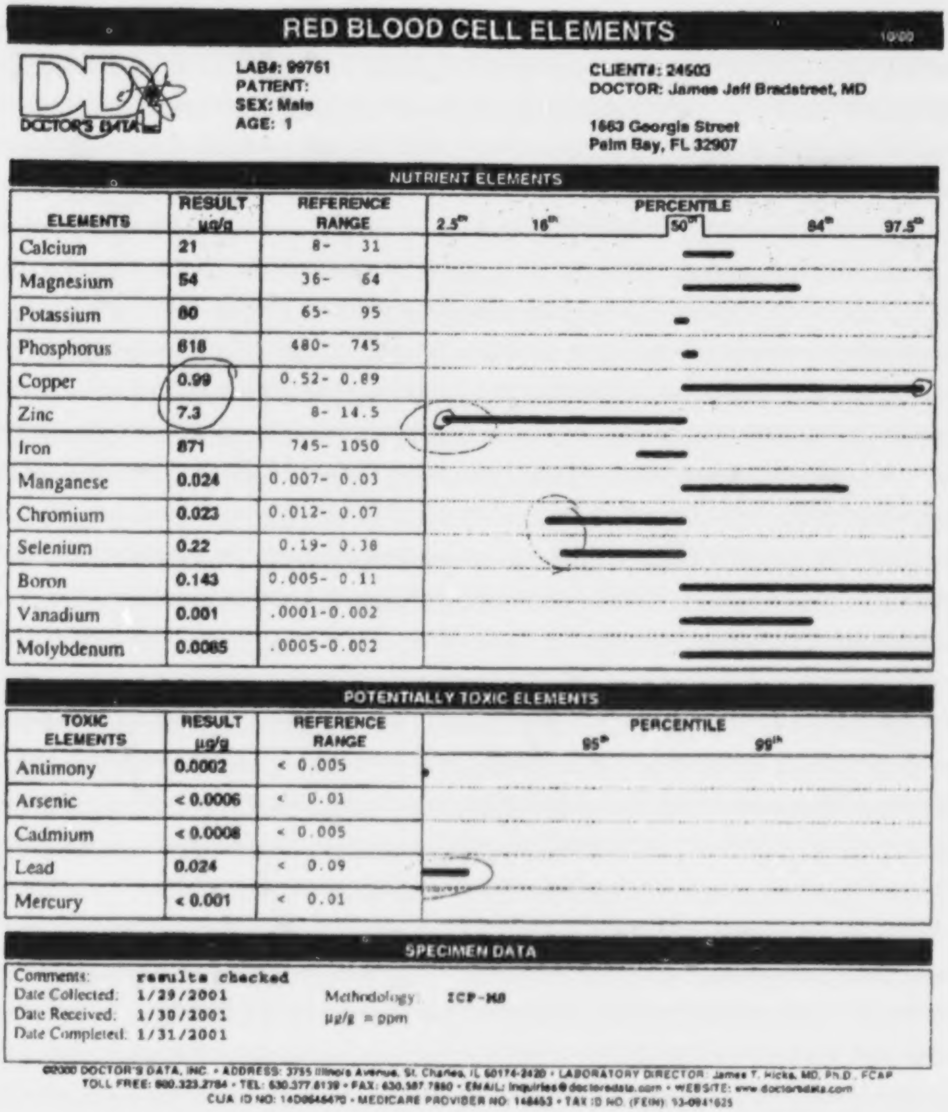

RED BLOOD CELL ELEMENTS

10/00

DOCTOR'S DATA

LAB#: 99761
PATIENT:
SEX: Male
AGE: 1

CLIENT#: 24503
DOCTOR: James Jeff Bradstreet, MD

1663 Georgia Street
Palm Bay, FL 32907

NUTRIENT ELEMENTS

ELEMENTS	RESULT µg/g	REFERENCE RANGE	PERCENTILE 2.5th 16th 50th 84th 97.5th
Calcium	21	8- 31	
Magnesium	54	36- 64	
Potassium	80	65- 95	
Phosphorus	618	480- 745	
Copper	0.99	0.52- 0.89	
Zinc	7.3	8- 14.5	
Iron	871	745- 1050	
Manganese	0.024	0.007- 0.03	
Chromium	0.023	0.012- 0.07	
Selenium	0.22	0.19- 0.38	
Boron	0.143	0.005- 0.11	
Vanadium	0.001	.0001-0.002	
Molybdenum	0.0085	.0005-0.002	

POTENTIALLY TOXIC ELEMENTS

TOXIC ELEMENTS	RESULT µg/g	REFERENCE RANGE	PERCENTILE 95th 99th
Antimony	0.0002	< 0.005	
Arsenic	< 0.0006	< 0.01	
Cadmium	< 0.0008	< 0.005	
Lead	0.024	< 0.09	
Mercury	< 0.001	< 0.01	

SPECIMEN DATA

Comments: results checked
Date Collected: 1/29/2001
Date Received: 1/30/2001
Date Completed: 1/31/2001
Methodology: ICP-MS
µg/g = ppm

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TOLL FREE: 800.323.2784 • TEL: 630.377.8139 • FAX: 630.587.7860 • EMAIL: inquiries@doctorsdata.com • WEBSITE: www.doctorsdata.com
CLIA ID NO: 14D0646470 • MEDICARE PROVIDER NO: 148453 • TAX ID NO. (FEIN): 93-0941625

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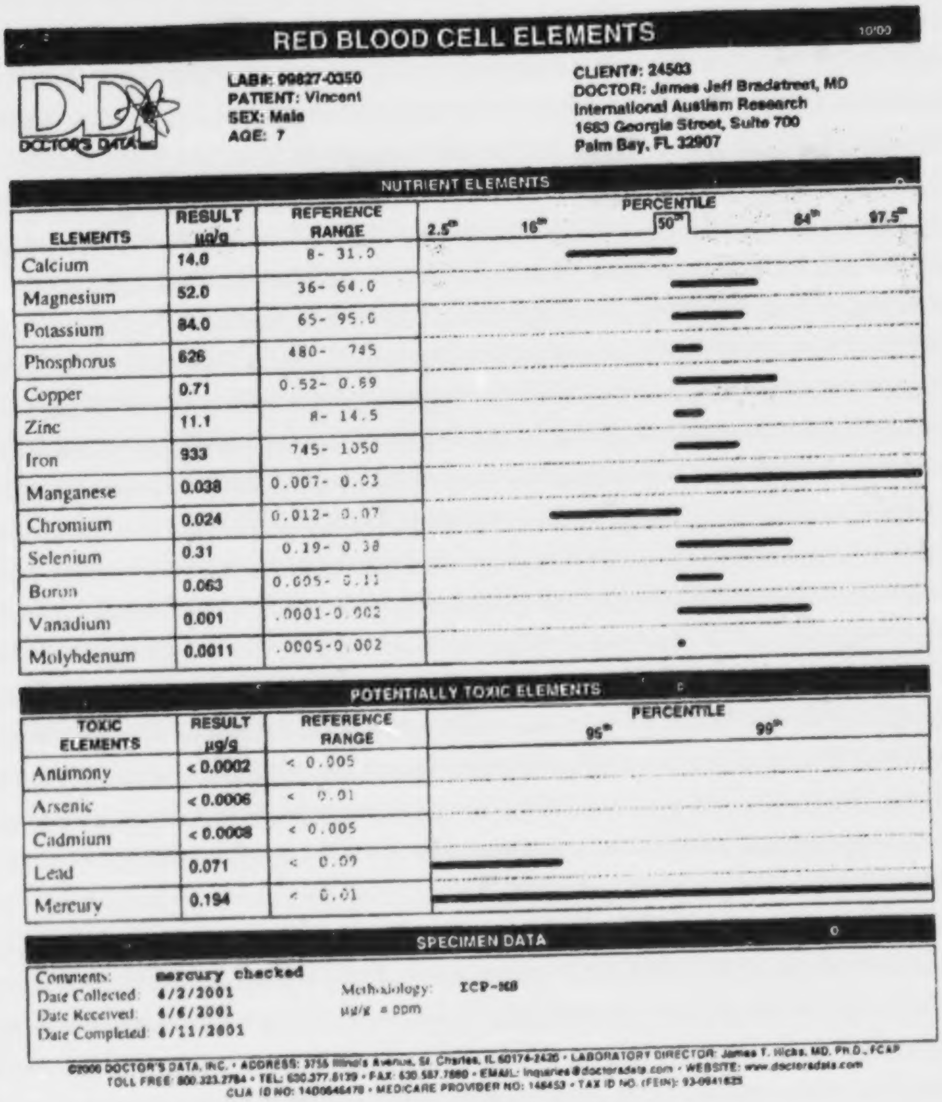

RED BLOOD CELL ELEMENTS

10/00

DOCTOR'S DATA

LAB#: 99827-0350
PATIENT: Vincent
SEX: Male
AGE: 7

CLIENT#: 24503
DOCTOR: James Jeff Bradstreet, MD
International Austism Research
1683 Georgia Street, Suite 700
Palm Bay, FL 32907

NUTRIENT ELEMENTS

ELEMENTS	RESULT µg/g	REFERENCE RANGE	PERCENTILE 2.5th 16th 50th 84th 97.5th
Calcium	14.0	8- 31.0	
Magnesium	52.0	36- 64.0	
Potassium	84.0	65- 95.0	
Phosphorus	626	480- 745	
Copper	0.71	0.52- 0.89	
Zinc	11.1	8- 14.5	
Iron	933	745- 1050	
Manganese	0.038	0.007- 0.03	
Chromium	0.024	0.012- 0.07	
Selenium	0.31	0.19- 0.38	
Boron	0.063	0.005- 0.11	
Vanadium	0.001	.0001-0.002	
Molybdenum	0.0011	.0005-0.002	●

POTENTIALLY TOXIC ELEMENTS

TOXIC ELEMENTS	RESULT µg/g	REFERENCE RANGE	PERCENTILE 95th 99th
Antimony	< 0.0002	< 0.005	
Arsenic	< 0.0006	< 0.01	
Cadmium	< 0.0008	< 0.005	
Lead	0.071	< 0.09	
Mercury	0.194	< 0.01	

SPECIMEN DATA

Comments: mercury checked
Date Collected: 4/2/2001
Date Received: 4/6/2001
Date Completed: 4/11/2001
Methodology: ICP-MS
µg/g = ppm

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CLIA ID NO: 14D0646470 • MEDICARE PROVIDER NO: 148453 • TAX ID NO. (FEIN): 93-0941635

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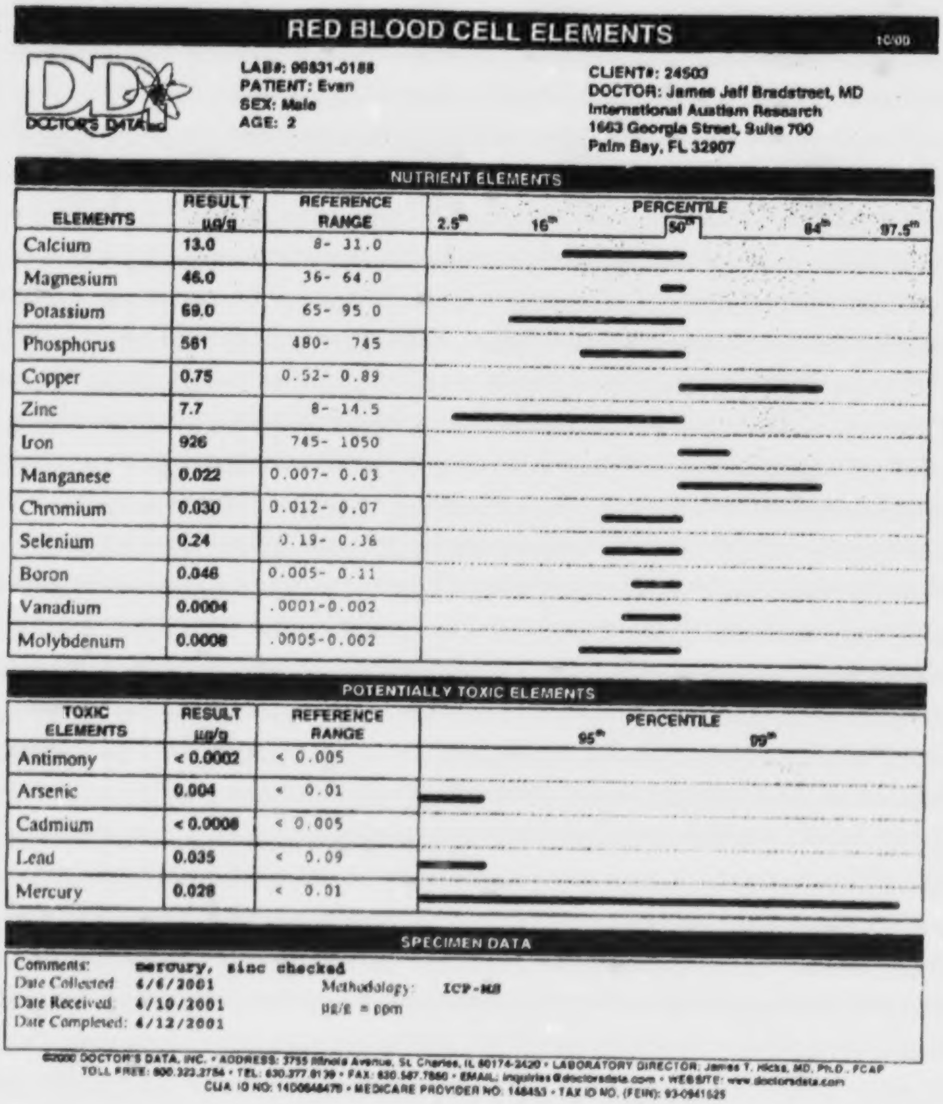

RED BLOOD CELL ELEMENTS

10/00

DOCTOR'S DATA

LAB#: 99831-0188
PATIENT: Evan
SEX: Male
AGE: 2

CLIENT#: 24503
DOCTOR: James Jeff Bradstreet, MD
International Austism Research
1663 Georgia Street, Suite 700
Palm Bay, FL 32907

NUTRIENT ELEMENTS

ELEMENTS	RESULT µg/g	REFERENCE RANGE	PERCENTILE 2.5th 16th 50th 84th 97.5th
Calcium	13.0	8- 31.0	
Magnesium	46.0	36- 64.0	
Potassium	69.0	65- 95.0	
Phosphorus	561	480- 745	
Copper	0.75	0.52- 0.89	
Zinc	7.7	8- 14.5	
Iron	926	745- 1050	
Manganese	0.022	0.007- 0.03	
Chromium	0.030	0.012- 0.07	
Selenium	0.24	0.19- 0.36	
Boron	0.046	0.005- 0.11	
Vanadium	0.0004	.0001-0.002	
Molybdenum	0.0008	.0005-0.002	

POTENTIALLY TOXIC ELEMENTS

TOXIC ELEMENTS	RESULT µg/g	REFERENCE RANGE	PERCENTILE 95th 99th
Antimony	< 0.0002	< 0.005	
Arsenic	0.004	< 0.01	
Cadmium	< 0.0008	< 0.005	
Lead	0.035	< 0.09	
Mercury	0.028	< 0.01	

SPECIMEN DATA

Comments: mercury, zinc checked
Date Collected 4/6/2001
Date Received 4/10/2001
Date Completed: 4/12/2001
Methodology: ICP-MS
µg/g = ppm

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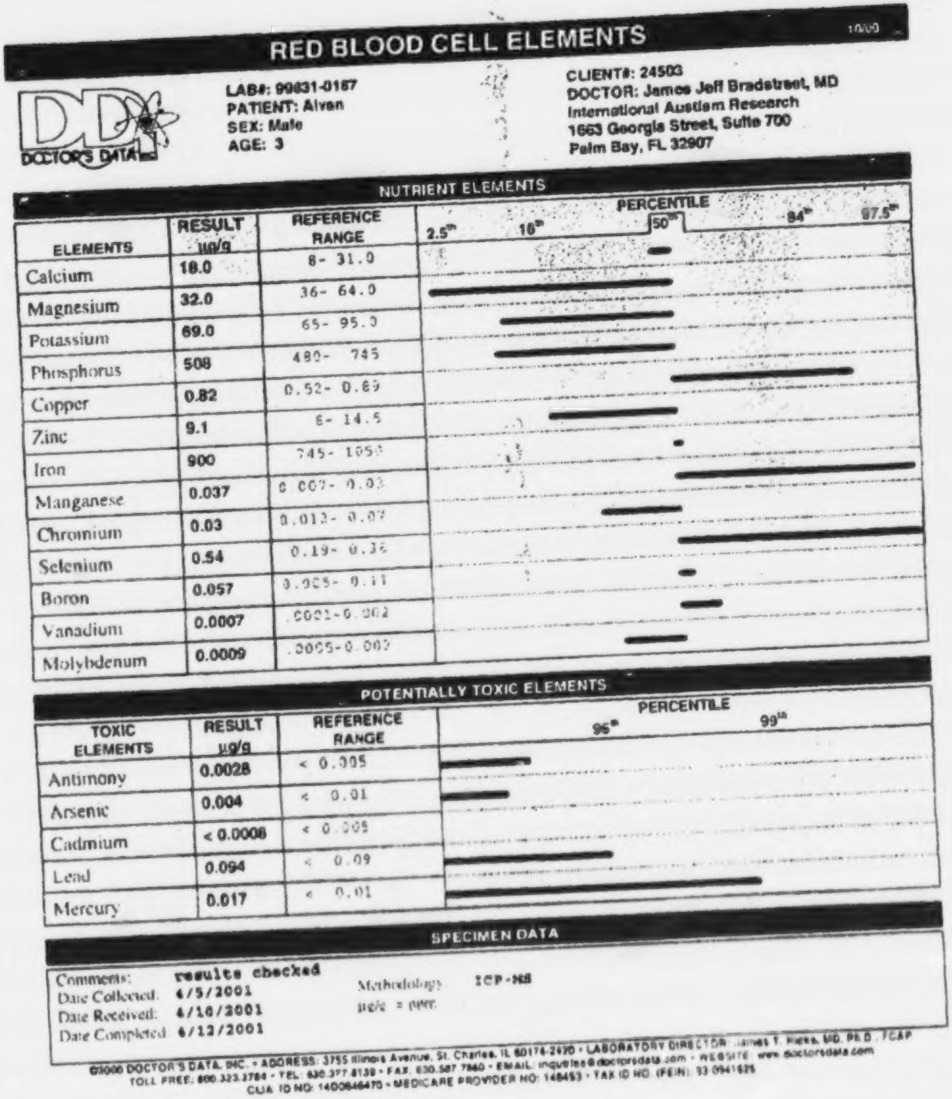

RED BLOOD CELL ELEMENTS

10/00

DOCTOR'S DATA

LAB#: 99631-0167
PATIENT: Alvan
SEX: Male
AGE: 3

CLIENT#: 24503
DOCTOR: James Jeff Bradstreet, MD
International Austism Research
1663 Georgia Street, Suite 700
Palm Bay, FL 32907

NUTRIENT ELEMENTS

ELEMENTS	RESULT µg/g	REFERENCE RANGE
Calcium	18.0	8- 31.0
Magnesium	32.0	36- 64.0
Potassium	69.0	65- 95.0
Phosphorus	508	480- 745
Copper	0.82	0.52- 0.89
Zinc	9.1	8- 14.5
Iron	900	745- 1050
Manganese	0.037	0.007- 0.03
Chromium	0.03	0.012- 0.07
Selenium	0.54	0.19- 0.36
Boron	0.057	0.025- 0.11
Vanadium	0.0007	.0001-0.002
Molybdenum	0.0009	.0005-0.002

POTENTIALLY TOXIC ELEMENTS

TOXIC ELEMENTS	RESULT µg/g	REFERENCE RANGE
Antimony	0.0028	< 0.005
Arsenic	0.004	< 0.01
Cadmium	< 0.0008	< 0.005
Lead	0.094	< 0.09
Mercury	0.017	< 0.01

SPECIMEN DATA

Comments: results checked
Date Collected: 4/5/2001
Date Received: 4/10/2001
Date Completed: 4/12/2001

Methodology: ICP-MS
µg/g = ppm

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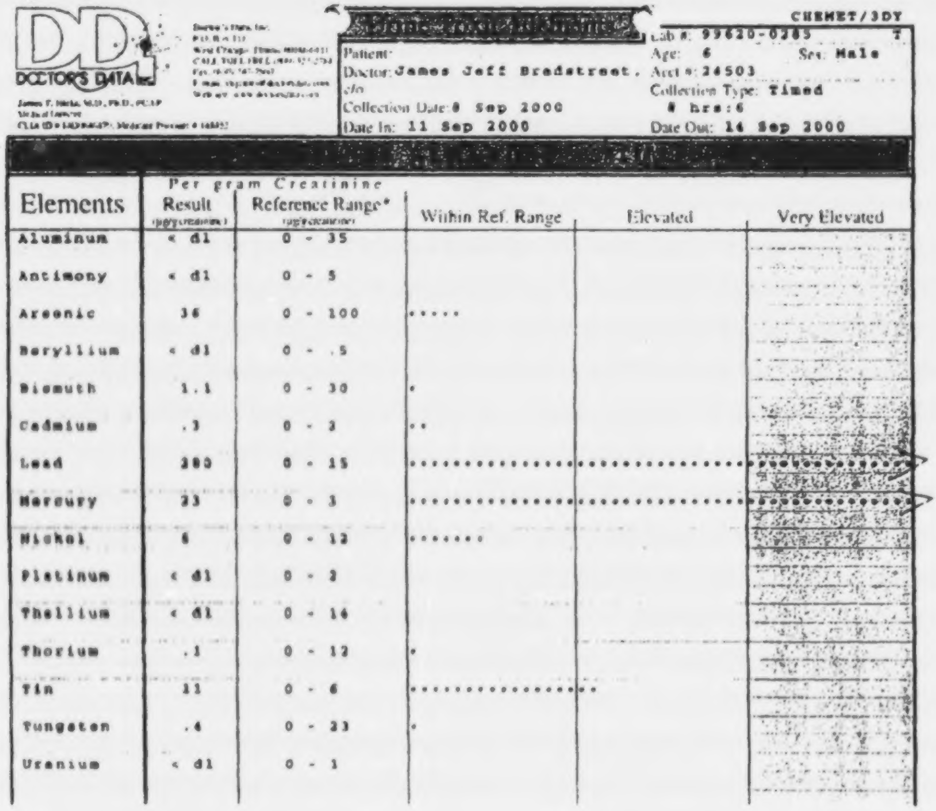
Family Toxic Metal Study

Starting with a 6 y.o. New Jersey boy with post-vaccinal decline into encephalopathy, following DMSA – Chemet® provocational challenge. The entire family was tested to determine potential local environmental influences. Only the child with autism was positive to increased post-provocational levels of mercury and lead. His younger brother was not vaccinated and has essentially normal levels.



DOCTOR'S DATA

CHEMET/3DY

Patient:	Lab #: 99620-0285 T
Doctor: James Jeff Bradstreet,	Age: 6 Sex: Male
c/o	Acct #: 24503
Collection Date: 8 Sep 2000	Collection Type: Timed # hrs: 6
Date In: 11 Sep 2000	Date Out: 14 Sep 2000

Elements	Per gram Creatinine Result (µg/g creatinine)	Reference Range* (µg/g creatinine)	Within Ref. Range	Elevated	Very Elevated
Aluminum	< dl	0 - 35			
Antimony	< dl	0 - 5			
Arsenic	36	0 - 100			
Beryllium	< dl	0 - .5			
Bismuth	1.1	0 - 30			
Cadmium	.3	0 - 2			
Lead	280	0 - 15			
Mercury	23	0 - 3			
Nickel	6	0 - 12			
Platinum	< dl	0 - 2			
Thallium	< dl	0 - 14			
Thorium	.1	0 - 12			
Tin	11	0 - 6			
Tungsten	.4	0 - 23			
Uranium	< dl	0 - 1			

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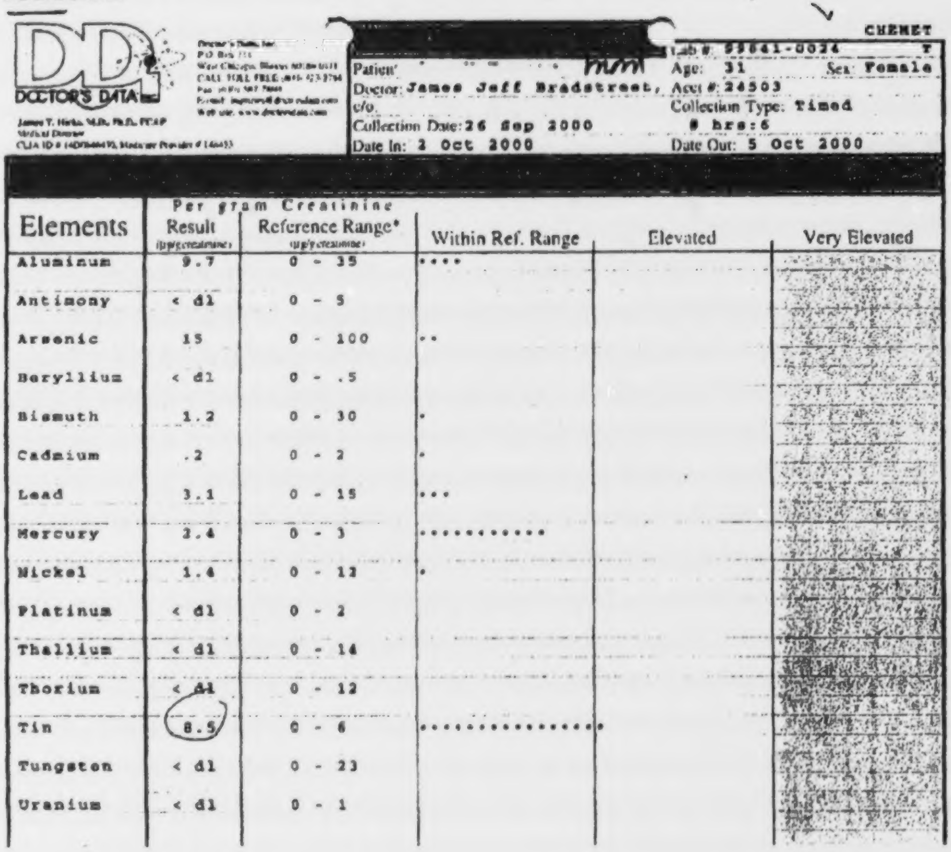
MOTHER



DOCTOR'S DATA

[redacted]

CHEMET

Patient: [redacted]	Lab #: 99841-0024 T
	Age: 31 Sex: Female
Doctor: James Jeff Bradstreet,	Acct #: 24503
c/o.	Collection Type: Timed
Collection Date: 26 Sep 2000	# hrs: 6
Date In: 2 Oct 2000	Date Out: 5 Oct 2000

[redacted]

Elements	Per gram Creatinine Result (µg/g creatinine)	Per gram Creatinine Reference Range* (µg/g creatinine)	Within Ref. Range	Elevated	Very Elevated
Aluminum	9.7	0 - 35	••••		
Antimony	< dl	0 - 5			
Arsenic	15	0 - 100	••		
Beryllium	< dl	0 - .5			
Bismuth	1.2	0 - 30	•		
Cadmium	.2	0 - 2	•		
Lead	3.1	0 - 15	•••		
Mercury	2.4	0 - 3	•••••••••••		
Nickel	1.4	0 - 12	•		
Platinum	< dl	0 - 2			
Thallium	< dl	0 - 14			
Thorium	< dl	0 - 12			
Tin	8.5	0 - 6	••••••••••••••••		
Tungsten	< dl	0 - 23			
Uranium	< dl	0 - 1	•		

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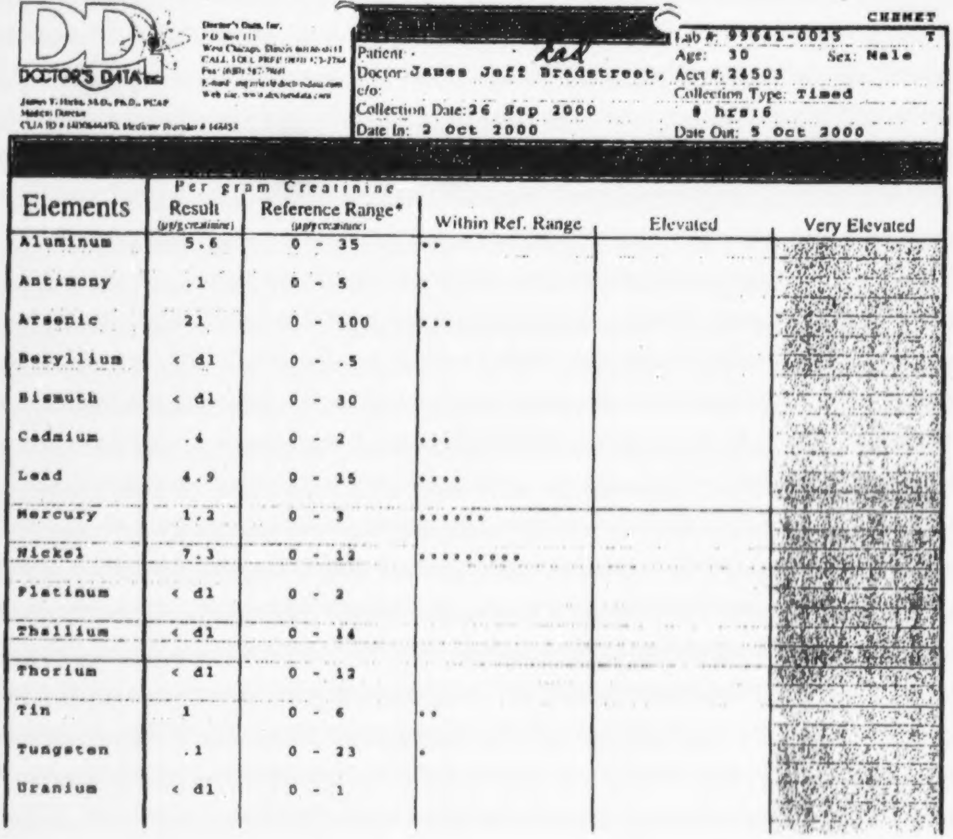
FATHER



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CHEMET

Lab #: 99641-0025 T
Patient: · dad
Age: 30 Sex: Male
Doctor: James Jeff Bradstreet, Acct #: 24503
c/o:
Collection Type: Timed
Collection Date: 26 Sep 2000
# hrs: 6
Date In: 2 Oct 2000
Date Out: 5 Oct 2000

Elements	Per gram Creatinine Result (µg/g creatinine)	Reference Range* (µg/g creatinine)	Within Ref. Range	Elevated	Very Elevated
Aluminum	5.6	0 - 35	••		
Antimony	.1	0 - 5	•		
Arsenic	21	0 - 100	•••		
Beryllium	< dl	0 - .5			
Bismuth	< dl	0 - 30			
Cadmium	.4	0 - 2	•••		
Lead	4.9	0 - 15	••••		
Mercury	1.2	0 - 3	••••••		
Nickel	7.3	0 - 12	•••••••••		
Platinum	< dl	0 - 2			
Thallium	< dl	0 - 14			
Thorium	< dl	0 - 12			
Tin	1	0 - 6	••		
Tungsten	.1	0 - 23	•		
Uranium	< dl	0 - 1			

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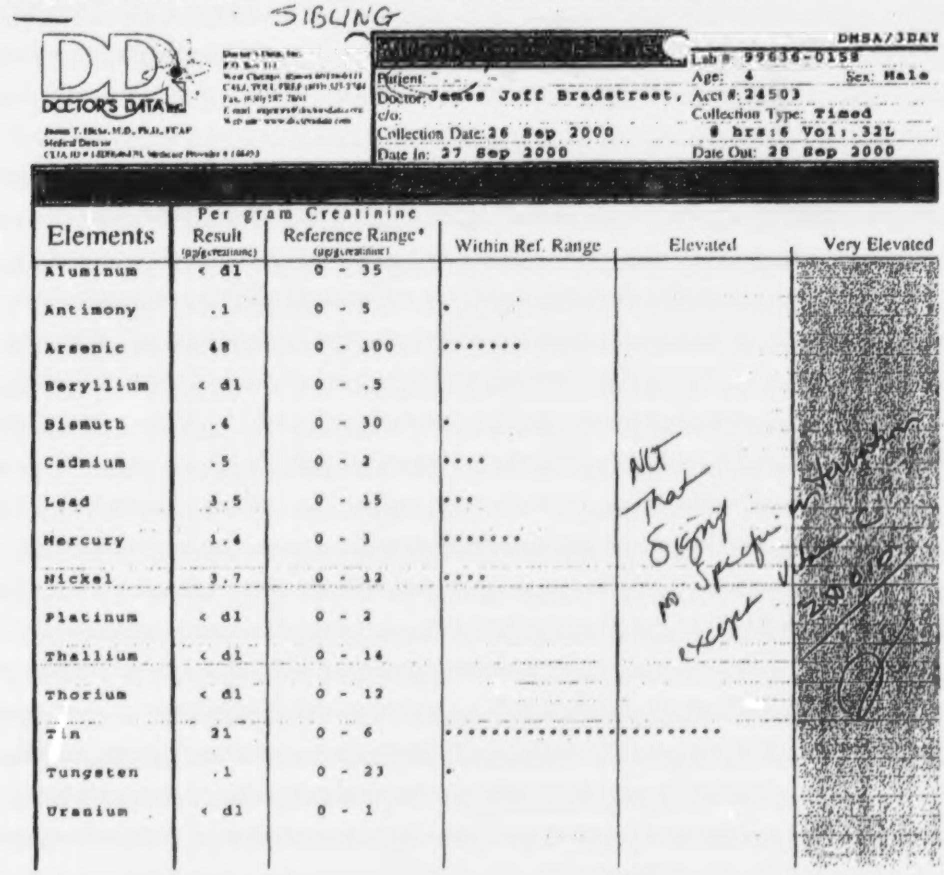
SIBLING AGE 4 NON-VACCINATED PER FAMILY DEMANDS



SIBLING

DOCTOR'S DATA inc.

[redacted]

DMSA/3DAY

Patient:

Doctor: James Jeff Bradstreet,

c/o:

Collection Date: 26 Sep 2000

Date In: 27 Sep 2000

Lab #: 99636-0158

Age: 4 Sex: Male

Acct #: 24503

Collection Type: Timed

hrs: 6 Vol: .32L

Date Out: 28 Sep 2000

[redacted]

Elements	Per gram Creatinine Result (µg/g creatinine)	Reference Range* (µg/g creatinine)	Within Ref. Range	Elevated	Very Elevated
Aluminum	< dl	0 - 35			
Antimony	.1	0 - 5	•		
Arsenic	48	0 - 100	•••••••		
Beryllium	< dl	0 - .5			
Bismuth	.6	0 - 30	•		
Cadmium	.5	0 - 2	••••		
Lead	3.5	0 - 15	•••		
Mercury	1.4	0 - 3	•••••••		
Nickel	3.7	0 - 12	••••		
Platinum	< dl	0 - 2			
Thallium	< dl	0 - 14			
Thorium	< dl	0 - 12			
Tin	21	0 - 6	••••••••••••••••	•••••••••••	
Tungsten	.1	0 - 23	•		
Uranium	< dl	0 - 1			

Not That Signif no Specific intervention except Vit C 2000

This above series points out several interesting findings. First, all member were given the exact same provocation agent and protocol. Mother, father and the unvaccinated sibling all have low levels of mercury excretion. The vaccinated child with autism however, has very high levels of both mercury and lead. So we can exclude environmental factors like water supply, mother's amalgams and dad's occupation. And we can assume the genetics are fairly even for the family as a risk, with the obvious point that genes do not make mercury or lead. So what is different? From all we can gather the only difference is the vaccine schedule of the autistic 6 year old. It would appear something in the vaccines damaged this child's toxic mineral defense system. Exactly what did it, I do not know – but we as a society need to investigate these types of occurrences.

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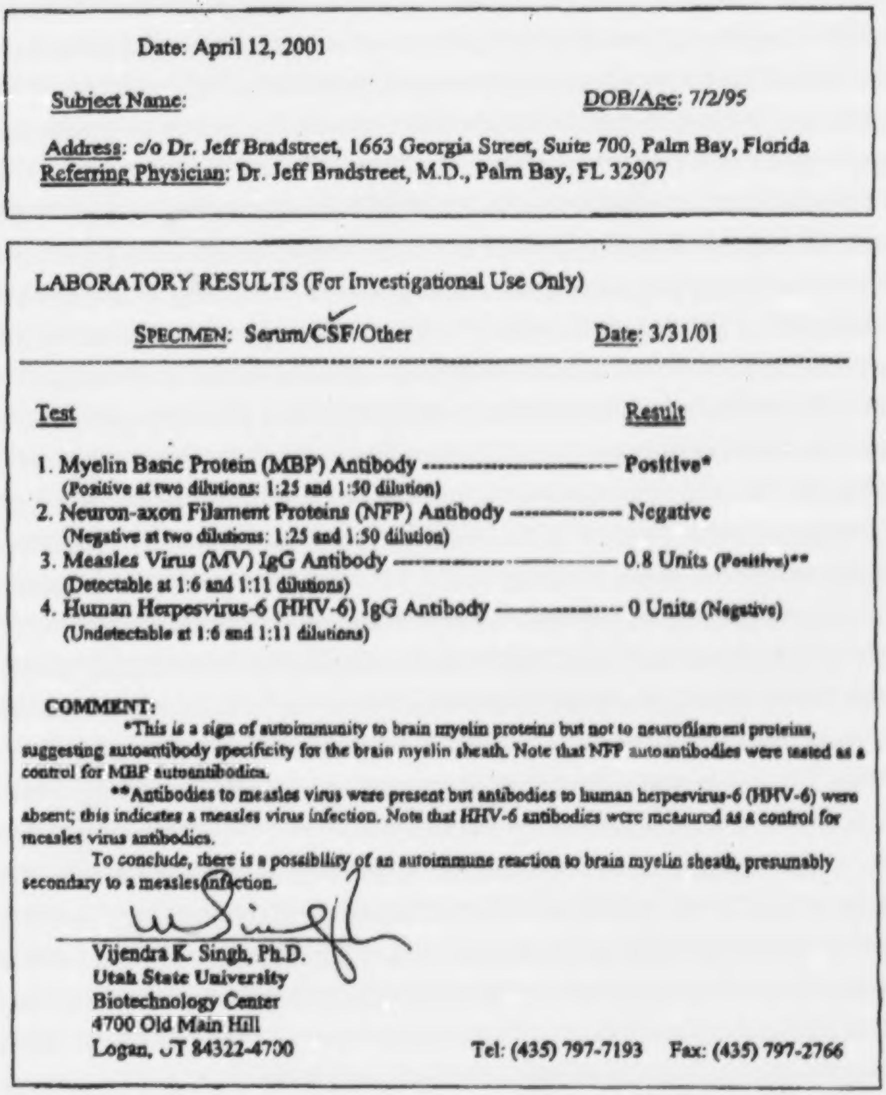
Critical Study of Cerebral Spinal Fluid Demonstrating the Expected Pattern of Post-Measles Autoimmune Encephalopathy. Persistent findings approximately 4 years after the MMR vaccine the parents believe precipitated his decline, Serum anti-MBP also positive and the serum Measles IgG was 22 standard deviations above the normally vaccinated child:



Date: April 12, 2001

Subject Name: DOB/Age: 7/2/95

Address: c/o Dr. Jeff Bradstreet, 1663 Georgia Street, Suite 700, Palm Bay, Florida
Referring Physician: Dr. Jeff Bradstreet, M.D., Palm Bay, FL 32907

LABORATORY RESULTS (For Investigational Use Only)

SPECIMEN: Serum/[✓ CSF]/Other Date: 3/31/01

Test — Result

1. Myelin Basic Protein (MBP) Antibody ---------------------- Positive*
   (Positive at two dilutions: 1:25 and 1:50 dilution)
2. Neuron-axon Filament Proteins (NFP) Antibody ------------ Negative
   (Negative at two dilutions: 1:25 and 1:50 dilution)
3. Measles Virus (MV) IgG Antibody ------------------------ 0.8 Units (Positive)**
   (Detectable at 1:6 and 1:11 dilutions)
4. Human Herpesvirus-6 (HHV-6) IgG Antibody -------------- 0 Units (Negative)
   (Undetectable at 1:6 and 1:11 dilutions)

COMMENT:

*This is a sign of autoimmunity to brain myelin proteins but not to neurofilament proteins, suggesting autoantibody specificity for the brain myelin sheath. Note that NFP autoantibodies were tested as a control for MBP autoantibodies.

**Antibodies to measles virus were present but antibodies to human herpesvirus-6 (HHV-6) were absent; this indicates a measles virus infection. Note that *HHV-6* antibodies were measured as a control for measles virus antibodies.

To conclude, there is a possibility of an autoimmune reaction to brain myelin sheath, presumably secondary to a measles infection.

Vijendra K. Singh, Ph.D.
Utah State University
Biotechnology Center
4700 Old Main Hill
Logan, UT 84322-4700

Tel: (435) 797-7193 Fax: (435) 797-2766

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ELECTROPHYSIOLOGICAL STUDIES REVEAL SIGNIFICANT ABNORMALITIES IN POST-VACCINAL ENEPHALOPATHY MALE AGE 6.5 POSITIVE ANTIBRAIN AUTOIMMUNITY POST MEALSES MUMPS RUBELLA VACCINE

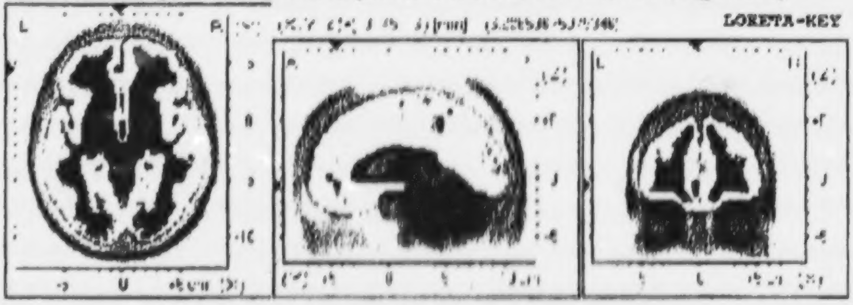
LORETA (Low Resolution Electromagnetic Tomographic Analysis)

Newly developed imaging technology with application to children.

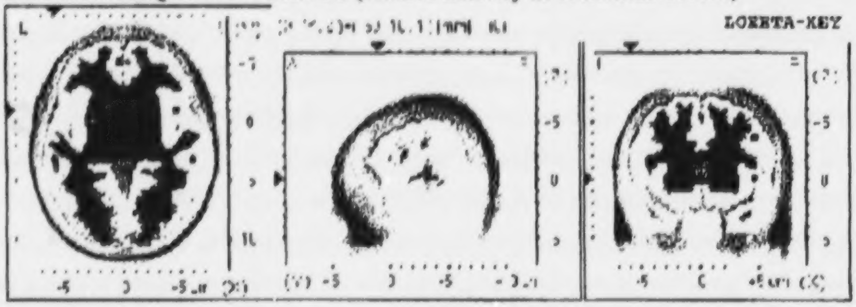
Maximum Activation Voxels Studies

Southeast Biofeedback Center, University of Tennessee
&
International Autism Research Center
J. Lubar, PhD & J. Bradstreet, MD

DELTA FREQUENCY BANDS (marked increase in anterior cingulated)



BETA 1 FREQUENCY BANDS (seizure activity in R insular cortex)



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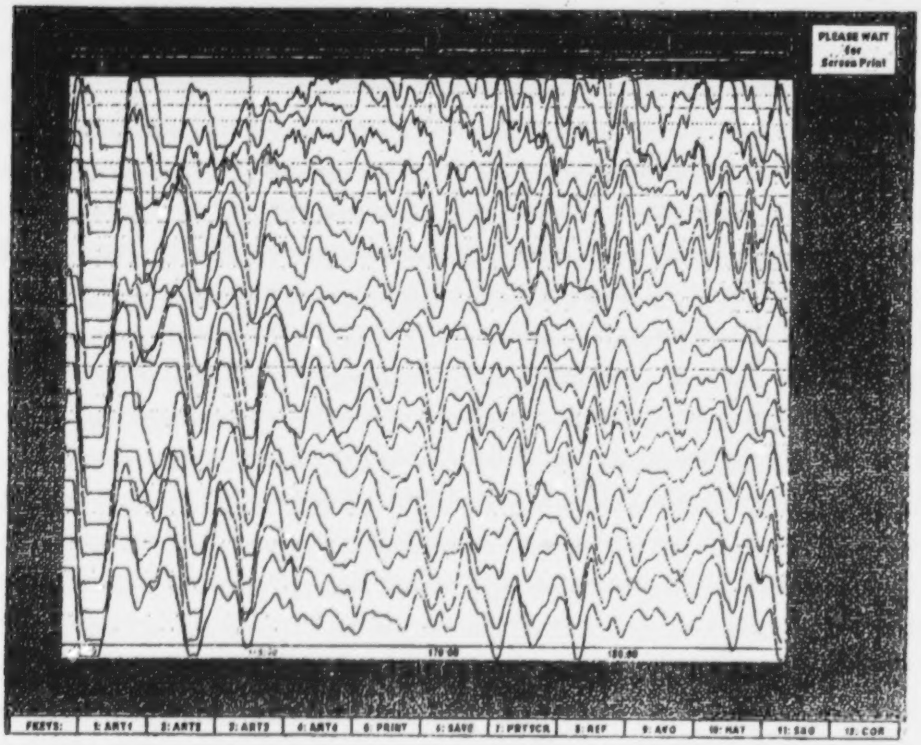
High Amplitude Slow Wave Activity – Seizure Equivalent Associated with Loss of Attention and Abnormal Behavior in the same child.



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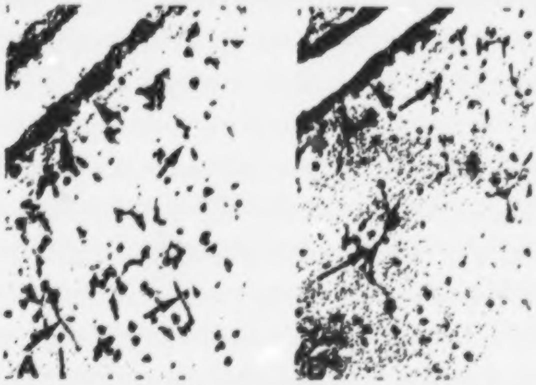
8: REF
9: AVG
12: COR

Representation of Anti-Endothelial – Anti-Brain Antibody Staining typical pattern observed in post MMR regression. Washington University, SL, Neuromuscular Lab.



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Summary of Observed Laboratory Findings:

I have included a synopsis of some typically abnormal laboratory findings in our patient population. To summarize the general findings we observe the estimated occurrences:

1) **Anti-Myelin Basic Protein Autoantbodies = 50 - 85%**
2) **Anti-Brain Endothelial (Vascular) Autoantibodies, form Anne Connolly' Lab at Washington University – Barnes Hosptial, St. Louis = 50%**
3) **Thrombophilia, coagulation disorders = 70%**
4) **Chronic Diarrhea or Constipation = 80%**
5) **Mercury Overload = 50 -70%**
6) **Omega 3 Fatty Acid Deficiency = 99%**
7) **Zinc Deficiency = 90%**
8) **Copper Excess = 90%**
9) **Elevated Serum or Whole Blood Serotonin = 60%**
10) **Immune Dysregulation = 90%**

Unfortunately, American gastroenterologists have been reluctant to perform endoscopy upon referral, so we have little independent data to corroborate the findings from the Royal Free Hospital Group. Of the 7 children evaluated, all (100%) were deemed to have ileolymphnoid hyperplasia and of the available measles TAQ-MAN PCR data available all are positive as well.

HYPOTHESIS FOR POST-VACCIINE AUTISM/ POST -VACCINAL ENCEPHALOPATHY

In discussing a model for autism one is faced with the heterogeneity of the condition. There is, however, a significant group of children with combined autoimmune brain disease, heavy metal exposure, thrombophilia, and autoimmune inflammatory bowel disease. So, for this group I believe the data fit the following general hypothesis.

1) **A genetically or environmentally predisposed child receives repeated exposure to thimerosal, aluminum and vaccine antigen components.**
2) **The mercury and aluminum with hepatitis B and HIB, induceTH-1/TH-2 imbalance favoring the development of autoimmunity and allergy.**
3) **Measles is a potent immune suppressor, which in the presence of the pre-existing TH-2 excess function allows for persistent vaccine strain infection, susceptibility to secondary infections and autoimmune encephalomyelitis (as documented in the section later on Measles and Immunosuppression.)**
4) **The persistence of measles in the child generates anti-myelin basic protein autoantibodies, which contribute to the decline in the child's behavior.**
5) **Mercury interferes with the normal development of myelin as well as other critical brain activities. Mercury also produces anti-MBP activity.**
6) **Measles viruses alter the cell surface protein expression on critical blood vessels and/or mercury damage these proteins so that either, additional**

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autoimmunity occurs as observed by Connolly, et al, J.Peds., May, 1999, and/or the coagulation system is activated.

7) Alterations of endothelial linings trigger thrombophilia reactions altering both blood flow and vascular tone secondary to inflammatory mediators. This also disrupts the normal blood brain barrier functions.
8) This creates abnormal regional blood flow in the brain and the gastrointestinal tract. Vasospasm presumably is triggered at the same time.
9) Altered and diminished blood flow causes cerebral dysfunction (language disorder, cognitive impairment, etc.)
10) Upregulation of coagulation may precipitate fibrous deposition in the perivascular regions of the brain, further impairing brain development.
11) Impaired vascular flow to the gut results in localized ischemia and impaired mucosal integrity – resulting in leaky gut syndrome.
12) The resultant increased flow of toxins into the hepatic-portal system overloads the liver detoxification systems, and furthers the encephalopathic problems through toxic exposure similar to what might be seen in liver failure, but distinct in its own pattern.
13) Injury to the kidney and toxic overload results in sulfur compound wasting as documented by: Sulphation deficit in "low-functioning" autistic children: a pilot study. *Biol Psychiatry* 1999 Aug 1;46(3):420-4.
14) Normal functioning of neurotransmitters is altered.
15) Seizures may occur from many of these disruptions.
16) Digestion of proteins and peptides is disrupted, allowing antigenic exposure, food allergies and exogenous opioid exposure. Secretin function is impaired.
17) Food allergy, caused by leaky gut, furthers the inflammatory changes in the gastrointestinal tract.
18) Opioids are generated from food peptides, which cannot be digested due to damage to DPP-VI enzyme system caused by mercury. Opioids interfere with neuronal migration and dopamine function.
19) Diarrhea and or constipation occur from inflammation of the GI tract due to both autoimmunity and ischemia.
20) Anerobic bacterial overgrowth produces toxins, which further interfere with function of the CNS.
21) Malabsorption of nutrients ensues and the child's ability to recover is impaired.

Many of these events occur almost simultaneously, so sequencing them in a linear fashion cannot demonstrate the full picture. Every one of these events has been documented in children with post-vaccinal encephalopathy, or as previously mentioned autism (a psychiatric term with little relevance to the biology).

The children we observe in our facility do not seem to represent an unusual distribution within the spectrum of autism. They come from all over the world, form every race and yet they still represent a common story. A child was well until a vaccine was administered and then the child began an abrupt decline into encephalopathy. Critics claim vaccines are safe, and that it is typical for autism to

occur between 12 and 24 months. Yet, historical evidence for this is lacking from the medical literature. Rather, older experts in the field of autism tell me it was previously a disorder recognized at or near birth.

This new variant of autism represents a distinct clinical syndrome where the potential for vaccine related constituents (mercury, aluminum, peptides and viruses) have more than a theoretical potentiality for causality.

Successful treatment will require addressing all these variables.

NEW DATA

Autism Spectrum Disorders and the Occurrences of Familial Thrombophilia Disorders – An Early Report

J.J. Bradstreet, & J.J. Katrzinel, The International Autism Research Center,
D. Berg, Hemex Laboratories, Phoenix, Arizona,
J. El-Dahr, Tulane University Medical Center

Paper Presented at the Defeat Autism Now! Conference November, 2000 San Diego, CA

Recently, growing evidence points to dysregulation of the immune system in Autism Spectrum Disorders (ASD). Various vaccines, viruses, pathogens, immune deficiencies, toxins, mercury, and autoantibodies have been put forward as playing a role in the development of autism related symptoms. Additionally, a familial or genetic tendency has been observed in this condition. Further, ASD has been shown to have an association with its own unique inflammatory bowel disease, characterized by nodular hyperplasia of the submucosal lymph nodes, thickening of the basement membrane and infiltration of delta-gamma T-lymphocytes. Thrombophilia is a propensity to form blood clots. Because thrombophilia disorders are also associated with immunological disorders, inflammatory bowel diseases, chronic fatigue/fibromyalgia disorders, and brain disorders including multiple sclerosis and cerebral palsy, it is reasonable to investigate the potential for thrombophilia in ASD. To determine this, nine families representing 10 children with ASD and 14 additional family members (13 parents and 1 sibling), selected at random from an ASD population were tested for coagulation disturbances. An Immune System Activation of Coagulation panel (ISAC) consisting of five tests including: Fibrinogen, Soluble Fibrin Monomer, Thrombin/Anti-Thrombin Complexes, Fragment 1+2, and Platelet Activation by flow cytometry were measured on all children and available family members. In the children with ASD seven of 10 were positive for at two markers of thrombophilia (ISAC), while 13 of 14 family members were positive as well. The families were further studied by an Hereditary Thrombosis Risk Panel (HTRP) consisting of AntiThrombin Activity, Protein C level, Protein S level, APC Resistance, Factor II Activity, Lipoprotein (a) levels, PAI-1 Activity and Homocysteine levels. In the children with ASD, six of 10 had abnormal findings in the HTRP and nine of 14 family members showed abnormal activated coagulation factors. By combining ISAC with HTRP, 10 of

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10 children with ASD were at risk for thrombophilia disorders and 13 of 14 family members were as well. Eleven of the family members reported symptoms consistent with CFS/Fibromyalgia. This represents a previously unreported high occurrence of familial thrombophilia where at least one member has ASD. The data provide further evidence of immune activation in ASD, which deserves additional study to determine the potential pathophysiological role of thrombophilia in the generation of autism related symptoms. Simultaneously, family members deserve careful evaluation for their own thrombophilia-associated conditions and risk factors.

Addendum: Since this presentation, approximately 60 additional families have been tested with similar results.

HIGH DOSE INTRAVENOUS IMMUNOGLOBULIN IMPROVES SYMPTOMS IN CHILDREN WITH AUTISM

J.J. Bradstreet, *International Autism Research Center, Palm Bay, FL*
V.K. Singh, *University of Michigan, Ann Arbor MI and* Utah State University, Salt Lake City, Utah & J.El-Dahr, *Tulane University Medical Center, New Orleans LA*

Presented at The International Symposium on Autism – Arnhem, Netherlands Dec. 28, 1999.

ABSTRACT: Although autism is likely a multifactorial disorder with diverse etiologies, evidence is accumulating that a combination of genetic predisposition, an environmental insult, and resulting alterations in immunity lead to the development of autoimmunity in many of the children who have a period of normal development and then develop autistic symptoms. Several authors using a variety of techniques have reported the presence of brain autoantibodies in these children. Children who undergo an autistic regression have a high rate of EEG abnormalities and have an even higher rate of brainwave abnormalities when examined by Magnetoencephalography, especially in the temporal lobes. Several authors have reported improvement in language and behavior with high dose IVIG in children with Landau-Kleffner syndrome or acquired epileptiform aphasia, a related disorder where a previously normal child loses speech accompanied by abnormal EEG findings. Low or "replacement" dose IVIG has been found to reduce autistic symptoms and improve speech in some children with autism, but has not been of benefit to the majority. With the hypothesis that autistic regression represents an autoimmune phenomenon, 13 children meeting diagnostic criteria for autism have received higher or "immunomodulatory" doses of IVIG. The children's ages ranged from 2.7-10.9 years (mean=5.8) with 10M and 3F. Twelve had normal immunoglobulin levels while one 9-year-old girl had borderline low IgG3 of 17 and a low IgA of 6. Nine of the 11 children who had antibodies to Myelin Basic Protein (MBP) measured were positive (82%) and of the 9 who had antibodies to Neuron-Axonal Filament Protein (NAFP) measured, 7 were positive (78%). The immunoglobulin dosage used has ranged from 1 to 2 gm/kg of IVIG given monthly. Four children have received one dose to date with limited follow up. Nine children have received multiple doses: 4 doses in 3 patients and 3 doses in 6 children. Eight of the 9 have made significant gains in language based on both the observations of the families and by improvements noted by therapists, teachers and the treating physician. Two of the children had been nonverbal and currently are speaking spontaneously. All children have been noted to make gains in relatedness and

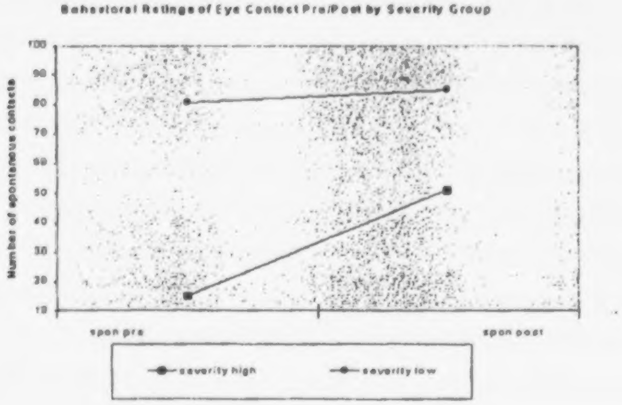
interaction. Improvements were found in the children negative for anti-MBP and/or anti-NAFP as well as in the children with demonstrable autoantibodies. One child, a 5-year-old boy who was verbal but had marked autistic features, normalized after one dose of 2 gm/kg and 3 doses of 1.5 gm/kg and is now considered a typical child and has been accepted into regular school. A 9-year-old boy who received 3 doses of 1 gm/kg now appears normal to his family with significant gains in language and social awareness. High dose IVIG appears to ameliorate the symptoms of children with autism at a higher rate than previous trials using lower doses. The positive results found in this open label trial of 1-2 gm/kg IVIG in children with autism should lead to a controlled trial in the future.

Eden Ft. Meyers/ IARC Study: Double Blind Controlled Study - Single Secretin Infusion in Children with ASD.

In 1999, we undertook to substantiate the observations of Mrs. V. Beck regarding her son and two other children treated with intravenous Ferring Secretin, or porcine derived neuropeptide, which normally stimulates the pancreas to produce bicarbonate after a meal. The drug/peptide is used in diagnostic evaluations by gastroenterologists. This was first reported in: *Assoc Acad Minor Phys* 1998;9(1):9-15 **Improved social and language skills after secretin administration in patients with autistic spectrum disorders.**

Horvath K,, et al . Department of Pediatrics, University of Maryland School of Medicine, Maryland, USA. (It has since been the subject of ongoing investigations and much controversy. Our findings support the original observations.)

In re-computing the analysis using high/low severity methodology we achieve - for spontaneous eye contacts behavioral ratings: 1) a significant difference between the groups (F=8.9, p<.01) meaning that they are two very different groups, 2) a significant improvement over the study (F=5.1, P.04) meaning the more severe patients improved more than the less severe. Graphically this is seen in Table 1.



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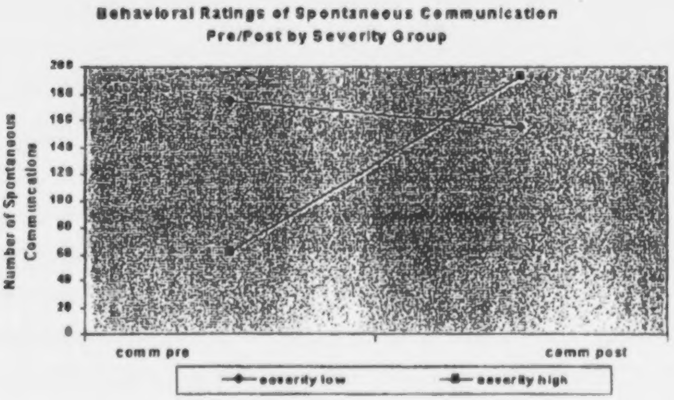
Eden/IARC Study Continued: In conducting the same sort of analysis for the Behavioral Rating of Spontaneous communication attempts we find that the two groups are not significantly different in elevation overall, but that there is a tread for there to be improvement over the study for both groups (F=3.8, p<.09), and a significant effect on interaction, again stating that the more severe patients improved significantly more than did the less severe patients (F=6.2, p<.04), as is graphically represented in Table 2.



Analysis: This data is consistent with observations by the Southwest Autism Research Center and the Recent Phase II trial with synthetic porcine Secretin by Repligen. Reference: www.repligen.com

Considerations for Treatment

The approach taken at the IARC is to minimize toxic elements hindering the child's own natural healing abilities, while simultaneously providing the nutritional support they are lacking. We also recommend a variety of therapies to address the mercury and autoimmune related sensory processing and motor skills defects observed in our population. Our approach seeks to discover the biological problems, and to correct them as we are able.

To do this we use one or more of the following:

- Elimination of gluten and casein containing foods, which results in improvement in about 80% of children (Cade et al, University of Florida, Shattock, University of Sunderlund, Reichlet, University of Oslo).
- Provision of normal gut flora such as lactobacillus.
- Essential fatty acids including Vitamin A from mercury-free cod liver oil.
- Magnesium and B6 for calming and constipation issues.
- Dysbiosis treatment – elimination of GI pathogens.

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- Zinc supplementation to boost the immune system and support myelinization.
- Clearing any impacted stool.
- Correction of any other apparent nutritional deficiencies.
- Oral immune globulin to support GI immunity and to clear persistent pathogens.
- Colostrum to add gut healingc factors - has lactoferrin to kill pathogens.
- Intravenous or Topical Secretin to promote pancreatic function and alkalinization of the gut - to heal and stimulate the GI tract.
- Mercury and/or lead detoxification with DMSA and supporting nutrients. DMSA may have other important detoxification effects.
- Oral, Transdermal, or Intravenous Reduced L-Glutathione to support the brain and liver detoxification pathways, stimulate the immune system and protect from mercury effects. Other sulfur sources to help this as well. (Taurine, Glucosamine Sulfate, MSM)
- L-Glutamine to promote epithelial health
- Correction of sleep disorders depending on the etiology. (Melatonin)
- A variety of sensory integration techniques.
- Applied Behavioral Analysis, verbal behavior and socially integrative behavioral therapies.
- Control of Seizures with medications and occasionally IVIG.
- Correction of immunoglobulin deficiency with IVIG.
- Elimination or control of autoimmunity with steroids, anti-inflammatories and/or IVIG.
- Correction of Thrombophilias with medically and nutritionally appropriate measures.
- Correction of Regional Cerebral Flow abnormalities with Aricept®, Nimotop® or other appropriate medications.
- Management of severe adverse symptoms with medications when necessary.(Risperdal, Prozac, Luvox, Celexa, etc)

As you can see practitioners, children and parents face daunting challenges in the management of the multiplicity of medical problems facing these children. We must support the parents and the children with the resources they require, while increasing physician awareness of the true extent of the biological issues. Many of these interventions are not covered by insurance or Medicaid

Prioritizing this list of options requires clinical experience and a lot of trial and error. Cookbook medicine has little application to this population. They are often unusually sensitive to ordinary vitamins, medicines, food colors and other additives. All of it requires a lot more testing and investigation to understand the best way to prioritize and edit this list.

A Brief Review of the Pertinent Medical Literature & References

These articles represent a fraction of the data, which can be gathered easily by any parent or physician by merely searching the National Library of Medicine Medline Database (http://www.ncbi.nlm.nih.gov/PubMed/). It is a free service of the American Taxpayer to the entire World. Unfortunately, most clinicians do not have the time or desire to perform this level of investigation – that is until they themselves have a child with a severe decline in functioning post a vaccine, or a determined parent finally forces the issue.

MERCURY RELATED ARTICLES

Exposure to methyl mercury results in serum autoantibodies to neurotypic and gliotypic proteins.

el-Fawal HA, Gong Z, Little AR, Evans HL
Neurotoxicology 1996 Spring;17(1):267-76 (review article)
Nelson Institute of Environmental Medicine, New York University Medical Center, Tuxedo Park 10987, USA.

Increased vulnerability of neurones and glial cells to low concentrations of methylmercury in a prooxidant situation.

Acta Neuropathol (Berl) 1998 Dec;96(6):621-7
Sorg O , Schilter B , Honegger P , Monnet-Tschudi F Institute of Physiology, Lausanne, Switzerland.

Abstract: Using reaggregating rat brain cell cultures at two different stages of differentiation, we examined the biochemical effects of a 10-day treatment with nanomolar concentrations of methylmercuric chloride (monomethylmercury), in the presence or absence of promoters of hydroxyl radical formation (10 microM copper sulphate plus 100 microM ascorbate). A decrease in total protein content accounted for the general cytotoxicity of these compounds, whereas selective effects were assessed by determining the activities of cell type-specific enzymes. Methylmercury, up to 100 nM, as well as the copper ascorbate mixture, when applied separately, induced no general cytotoxicity, and only slight effects on neuronal parameters. However, when applying 100 nM methylmercury and the copper-ascorbate mixture together, a drastic decrease in neuronal and glial parameters was found. **These results suggest that in prooxidant conditions low doses of mercury can become much more deleterious for the central nervous system.**

Toxicity of mercury.

J Hum Hypertens 1999 Oct;13(10):651-6
Langford N , Ferner R West Midlands Centre for Adverse Drug Reaction Reporting, City Hospital, Dudley Road, Birmingham B18 7QH, UK.

Abstract: A ruling by the European Union heralds the demise of those useful clinical instruments, the mercury thermometer and the sphygmomanometer. The new laws have been passed because of worries about mercury poisoning. There are three forms of mercury from a toxicological point of view: inorganic mercury salts; organic mercury compounds; and metallic mercury. Inorganic mercury salts are water soluble, irritate the gut, and cause severe kidney damage. **Organic mercury compounds, which are fat soluble, can cross the blood brain barrier and cause neurological damage. Mercury easily crosses into the brain, and causes tremor, depression, and behavioural disturbances.**

Synergistic effects of some metals contaminating mussels on the cytotoxicity of the marine toxin okadaic acid.

Arch Toxicol 1999 Aug;73(6):289-95
Traore A, Bonini M, Dano SD, Creppy EE.

Laboratory of Toxicology and Applied Hygiene, Faculty of Pharmaceutical Sciences, University Victor Segalen Bordeaux 2, 146, rue Leo-Saignat, F-33076 Bordeaux, France.

Okadaic acid (OA), a marine toxin is cytotoxic and promotes tumours in mouse skin. It is a specific and potent inhibitor of protein synthesis and also inhibits phosphatases A1 and A2 in vitro. In the present study, we investigated the influence of metals found at acceptable levels in mussels as environmental pollutants on the cytotoxicity of OA in Vero cells. Among the metals found in mussels (Mytilus edulis), the most represented, in terms of molar quantities per gram of dried weight are aluminium (230 nmol/g), copper (58 nmol/g), lead (16 nmol/g), mercury (14 nmol/g) and cadmium (7.4 nmol/g). A solution containing these five metals Al(3+), Cu(2+), Pb(2+), Hg(2+) and Cd(2+) combined at the concentrations detected in mussels, stimulated protein synthesis (+25%, $P < 0.01$), whereas different dilutions of this solution in the presence of okadaic acid (15 ng/ml, i.e. 18.7 x 10(-9) M) increased the percentage of protein synthesis inhibition from 35 to 79%. The metals also increased the lactate dehydrogenase (LDH) release into the medium and the lipid peroxidation induced by this algal toxin. In addition, these metals reduced the cell viability for an incubation period of 24 h especially at the two higher concentrations. **These results indicate that metals (Al(3+), Cu(2+), Pb(2+), Hg(2+), Cd(2+)) in concentration ranges largely below the acceptable levels, synergistically increase the cytotoxicity of low concentrations of OA in cultured cells.**

Interaction of metals and thiols in cell damage and glutathione distribution: potentiation of mercury toxicity by dithiothreitol.

Toxicology 2001 Jan 2;156(2-3):93-100
Hultberg B, Andersson A, Isaksson A.

Department of Clinical Chemistry, Institute of Laboratory Medicine, University Hospital, S-22185 Lund, Sweden.

In the present study, we have investigated the effects of extracellular redox status and metal/thiol interactions on glutathione distribution in HeLa cell cultures. No effects were seen on glutathione distribution after the addition of different thiols, whereas the pro-oxidant copper ions affected glutathione distribution in several ways. The addition of dithiothreitol (DTT) but not the other thiols potentiated the effects of mercury ions on glutathione distribution and cell toxicity. **In the presence of DTT, increased intra- and extracellular glutathione concentrations were noted already at 0.05 micromol/l, which was below the previously reported toxicity threshold for mercury ions in blood. Likewise DTT potentiated the effects of copper ions on glutathione distribution and cell toxicity**, whereas the addition of DTT to cell cultures with a non-metal thiol reactive agent (hydroquinone) or an oxidative agent (hydrogen peroxide) did not affect glutathione distribution or cell toxicity. Thus, it seems as the synergistic effects between DTT and thiol reactive agents only apply to metal ions.

(This important report – above - shows that both copper and mercury share a common pathway in toxicity and that DDT makes either more cytotoxic. Again the combined subthreshold toxicities of several intoxicants combine to become very toxic when present in the same child. The implication for epidemiology is profound. Clusters of autism may well be due to complex environmental factors, household pesticide use, thimerasol and other factors. This makes it even more important to remove mercury from vaccines.)

Neonatal induction of tolerance to T(h)2-mediated autoimmunity in rats.
Field AC, Caccavelli L, Fillion J, Kuhn J, Mandet C, Druet P, Bellon B
Int Immunol 2000 Oct;12(10):1467-77

Contribution of H-2 and non-H-2 genes in the control of mercury-induced autoimmunity.
Abedi-Valugerdi M, Moller G *Int Immunol* 2000 Oct;12(10):1425-30

Specific inhibition of rRNA transcription and dynamic relocation of fibrillarin induced by mercury.
Chen M, von Mikecz A
Exp Cell Res 2000 Aug 25;259(1):225-38

Cytokine regulation of a rodent model of mercuric chloride-induced autoimmunity.
Bagenstose LM, Salgame P, Monestier M
Environ Health Perspect 1999 Oct;107 Suppl 5:807-10

Neuroimmunotoxicology: humoral assessment of neurotoxicity and autoimmune mechanisms.
El-Fawal HA, Waterman SJ, De Feo A, Shamy MY
:*Environ Health Perspect* 1999 Oct;107 Suppl 5:767-75

Murine mercury-induced autoimmunity: a model of chemically related

autoimmunity in humans.
Bagenstose LM, Salgame P, Monestier M *Immunol Res* 1999;20(1):67-78
Experimental studies on genetically determined susceptibility to mercury-induced autoimmune response.
Nielsen JB, Hultman P
Ren Fail 1999 May-Jul;21(3-4):343-8

Mechanism of mercury-induced autoimmunity: both T helper 1- and T helper 2-type responses are involved.
Hu H, Moller G, Abedi-Valugerdi M
Immunology 1999 Mar;96(3):348-57

Mercury intolerance and lymphocyte transformation test with nickel sulfate, palladium chloride, mercuric chloride, and gold sodium thiosulfate.
Environ Res 2000 Oct;84(2):140-4
Cederbrant K, Gunnarsson LG, Marcusson JA.

The frequency of mercury intolerance in patients with chronic fatigue syndrome and healthy controls.
Contact Dermatitis 1999 Jul;41(1):60-1

Thimerosal positivities: the role of organomercury alkyl compounds.
Contact Dermatitis 1998 Jun;38(6):325-8
Santucci B, Cannistraci C, Cristaudo A, Camera E, Picardo M.

Articles Related to Viral Autoimmunity

Induction of autoimmune reactions to myelin basic protein in measles virus encephalitis in Lewis rats.
Liebert UG, Linington C, ter Meulen V
J Neuroimmunol 1988 Jan;17(2):103-18

Autoimmune reactions against myelin basic protein induced by corona and measles viruses.
ter Meulen V.
Ann N Y Acad Sci 1988;540:202-9

Autoimmunity caused by host cell protein-containing viruses.
Med Microbiol Immunol (Berl) 1994 Sep;183(4):195-204
Rott O, Herzog S, Cash E.

Characterization of measles virus-induced cellular autoimmune reactions against myelin basic protein in Lewis rats.

J Neuroimmunol 1990 Sep-Oct;29(1-3):139-47
Liebert UG, Hashim GA, ter Meulen V.

Paramyxovirus membrane protein enhances antibody production to new antigenic determinants in the actin molecule: a model for virus-induced autoimmunity.

J Virol 1990 Jul;64(7):3179-84
Anomasiri WT, Tovell DR, Tyrrell DL

Presentation of the self antigen myelin basic protein by dendritic cells leads to experimental autoimmune encephalomyelitis.

J Immunol 1999 Jul 1;163(1):32-9
Dittel BN , Visintin I , Merchant RM , Janeway CA Jr Section of Immunobiology, Yale University School of Medicine, Howard Hughes Medical Institute, New Haven, CT 06510,

Abstract: Bone marrow (BM)-derived dendritic cells (DC) are potent stimulators of naïve CD4+ T cell activation. Because DC are efficient at Ag processing and could potentially present self Ags, **we investigated the role of DC in the presentation of an encephalitogenic peptide from myelin basic protein (Ac1-11) in the induction of experimental autoimmune encephalomyelitis (EAE).** To determine if DC could prime for EAE, we transferred DC pulsed with Ac1-11 or with medium alone into irradiated mice in combination with CD4+ T cells isolated from a mouse transgenic for a TCR specific for Ac1-11 + I-Au. Mice transferred with Ac1-11-pulsed DC developed EAE 7-10 days later, whereas mice receiving medium-pulsed DC did not. By day 15, all mice given peptide-loaded DC had signs of tail and hind limb paralysis, and by day 20 infiltration of Ac1-11-specific CD4+ T cells was detected in the brain parenchyma. We also demonstrated interactions between Ac1-11-pulsed DC and Ac1-11-specific T cells in the lymph nodes 24 h following adoptive transfer of both cell populations. These data show that DC can efficiently present the self Ag myelin basic protein Ac1-11 to Ag-specific T cells in the periphery of mice to induce EAE.

Brain-gut axis and mucosal immunity: a perspective on mucosal psychoneuroimmunology.

Semin Gastrointest Dis 1999 Jan;10(1):8-13
Department of Medicine, National University of Ireland, and Cork University Hospital.

Abstract: The role of the brain-gut axis has traditionally been investigated in relation to intestinal motility, secretion, and vascularity. More recently, the concept of brain-gut dialogue has extended to the relationship between the nervous system and mucosal immune function. There is compelling evidence for a reciprocal or bi-directional communication between the immune system and the neuroendocrine system. This is mediated, in part, by shared ligands (chemical messengers) and receptors that are common to the immune and nervous systems. Although the concept of psychoneuroimmunology and neuroimmune cross-talk has been studied primarily in the context of the systemic immune system, it is likely to have special significance in the gut. The mucosal immune system is anatomically, functionally, and operationally distinct from the systemic immune system and is subject to independent regulatory signals. Furthermore, the intestinal mucosal immune system operates in a local milieu that depends on a dense innervation for its integrity, with juxtaposition of neuroendocrine cells and mucosal immune cells. **An overview of evidence for the biologic plausibility of a brain-gut-immune axis is presented and its potential relevance to mucosal inflammatory disorders is discussed.**

Transient virus infection and multiple sclerosis.

Rev Med Virol 2000 Sep-Oct;10(5):291-303

Atkins GJ, McQuaid S, Morris-Downes MM, Galbraith SE, Amor S, Cosby SL, Sheahan BJ.

Department of Microbiology, Moyne Institute of Preventive Medicine, Trinity College,

Multiple sclerosis (MS) is a chronic, demyelinating disease of the CNS in which autoimmunity to myelin plays a role in pathogenesis. The epidemiology of MS indicates that it may be triggered by a virus infection before the age of adolescence, but attempts to associate a specific virus with MS have produced equivocal results. Many studies of the aetiology of MS have postulated that a persistent virus infection is involved, but transient virus infection may provide a plausible alternative mechanism that could explain many of the inconsistencies in MS research. The most studied animal model of MS is chronic relapsing experimental autoimmune encephalomyelitis (CREAE), which is induced in susceptible animals following injection of myelin components. While CREAE cannot provide information on the initiating factor for MS, it may mimic disease processes occurring after an initial trigger that may involve transient virus infection. The disease process may comprise separate triggering and relapse phases. **The triggering phase may involve sensitisation to myelin antigens as a result of damage to oligodendrocytes or molecular mimicry. The relapse phase could be similar to CREAE, or alternatively relapses may be induced by further transient virus infections which may not involve infection of the CNS, but which may involve the recrudescence of anti-myelin autoimmunity. Although current vaccines have a high degree of biosafety, it is suggested that the measles-mumps-rubella vaccine in particular could be modified to obviate any possibility of triggering anti-myelin autoimmunity.**

(This is a statement which parallels the logic V.K. Singh and I believe is the underlying pathophysiological mechanism of the post MMR autoimmunity we see.)

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Articles related to Measles Virus Induced Immune Suppression

(with my comments about critical articles)

Measles virus infection in a transgenic model: virus-induced immunosuppression and central nervous system disease.

Cell 1999 Sep 3;98(5):629-40

Oldstone MB, Lewicki H, Thomas D, Tishon A, Dales S, Patterson J, Manchester M, Homann D, Naniche D, Holz A.

Department of Neuropharmacology, The Scripps Research Institute, La Jolla, California 92037, USA. mbaobo@scripps.edu

Measles virus (MV) infects 40 million persons and kills one million per year primarily by suppressing the immune system and afflicting the central nervous system (CNS). The lack of a suitable small animal model has impeded progress of understanding how MV causes disease and the development of novel therapies and improved vaccines. We tested a transgenic mouse line in which expression of the MV receptor CD46 closely mimicked the location and amount of CD46 found in humans. Virus replicated in and was recovered from these animals' immune systems and was associated with suppression of humoral and cellular immune responses. Infectious virus was recovered from the CNS, replicated primarily in neurons, and spread to distal sites presumably by fast axonal transport. Thus, a small animal model is available for analysis of MV pathogenesis.

(My note: this points out the importance of appropriate vaccine policies as well the presumed mechanism whereby vaccine strain viruses may be causing immunosuppression and persistent infections.)

Measles virus infection causes transient depletion of activated T cells from peripheral circulation.

J Clin Virol 1999 May;12(3):201-10

Nanan R, Chittka B, Hadam M, Kreth HW.

Universitats-Kinderklinik Wurzburg, Germany. kink106@mail.uni.wuerzburg.de

BACKGROUND: **Natural measles virus infection as well as vaccination with attenuated measles virus induce temporary immunosuppression, which is responsible for part of the morbidity and mortality associated with measles.** The underlying molecular mechanisms are not known. Recently, in vitro studies have revealed a marked increase of LFA-1 expression of lymphocytes in the presence of infectious measles virus. OBJECTIVES: In order to further investigate immune dysfunction in measles we analyzed the expression of leukocyte function-associated antigen 1 (LFA-1) on ex vivo derived circulating human T cells. Study design: Expression of LFA-1 was measured by flow cytometry using monoclonal antibodies directed against CD11a and CD18. LFA-1 expression was followed in the course of infection in four adult seronegative vaccinees and in four patients with natural measles. RESULTS: **There was a remarkable loss of LFA-1-bright cells during natural measles and after measles vaccination.** The number of LFA-1-bright cells reached a minimum on day 7-14 after vaccination, and at the onset of rash during natural measles infection, and approached normal levels within 3-5 weeks. CONCLUSION: **It is suggested that measles virus infection interferes with lymphocyte trafficking and reallocation. Disruption of recirculation and random homing of lymphocytes might contribute to the immunosuppression, which is characteristic for measles virus infection.**

(My Note: This provides further support that the vaccine strain is capable of immune suppression and that this effect is indistinguishable from the wild strains. This adds to the concerns that the vaccine can cause the various disorders it has been created to prevent. It also adds to the concerns about providing MMR in combination and to a sickly child.)

Changes within T cell receptor V beta subsets in infants following measles vaccination.

Clin Immunol Immunopathol 1996 May;79(2):163-70

Auwaerter PG, Hussey GD, Goddard EA, Hughes J, Ryon JJ, Strebel PM, Beatty D, Griffin DE.

Division of Infectious Diseases, Department of Medicine, John Hopkins University School of Medicine, Baltimore, MD 21287, USA.

Measles produces immune suppression which contributes to an increased susceptibility to other infections. Recently, high titered measles vaccines have been linked to increased long-term mortality among some female recipients. Because the mechanisms by which wild-type or attenuated live-vaccine strains of measles virus alter subsequent immune responses are not fully understood, this prompted an examination of the changes within the peripheral blood T cell receptor V beta repertoire following measles immunization. Twenty-four 6- and 9-month-old infants were studied at 2 weeks and 3 months following immunization by semiquantitative reverse transcription-polymerase chain reaction. There was a significant increase in V beta 2 expression (P less than 0.05), and a decrease in the V beta 4 subset (P less than 0.03) 2 weeks following vaccination with subsequent return to baselines at 3 months in vaccine recipients who seroconverted. These data suggest that measles virus may affect immune responses in part by altering the T cell receptor repertoire.

(This documents the critical interactions between the immunosuppressive effects of vaccine measles virus and the protracted immune suppression, which will follow

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vaccination. Therefore, a consequence of the vaccine – in addition to the direct measles infection is the immunosuppression and other viral/bacterial/fungal infections, which may ensue.)

Antibody response to measles-mumps-rubella vaccine of children with mild illness at the time of vaccination.

JAMA 1996 Mar 6;275(9):704-7

King GE, Markowitz LE, Heath J, Redd SC, Coleman S, Bellini WJ, Sievert A.

National Immunization Program, Centers for Disease Control and Prevention, Atlanta, GA 30333 USA.

OBJECTIVE: To examine the response to measles-mumps-rubella (MMR) vaccine among children with and without mild illness. DESIGN: Prospective cohort. PARTICIPANTS: A total of 386 children aged 15 to 23 months. MAIN OUTCOME MEASURES: Seroconversion rates to measles, mumps, and rubella in ill and well children. SETTING: Six public health immunization clinics in two counties in the greater metropolitan Atlanta, Ga, area from February 1992 to April 1993. RESULTS: Acute upper respiratory tract infection, otitis media, and diarrhea were observed in 128 (33%), 41 (11%), and 13 (3%) of the children (groups are not mutually exclusive); 157 children had one of these mild illnesses and 229 were well. Overall seroconversion rates were 98% for measles, 83% for mumps, and 98% for rubella antigens. Measles seroconversion rates for ill children compared with well children, respectively, were as follows: upper respiratory tract infection, 99% vs 97%; mild fever, 98% vs 97%; otitis media, 98% vs 98%; diarrhea, 100% vs 98%; and any mild illness, 99% vs 97%. Estimates of the magnitude of antibody response to measles, mumps, and rubella antigens were the same for children with and without mild illness. There was no association of mild illness with increased rates and severity of adverse events reported in the 2 weeks after vaccination. CONCLUSIONS: Vaccinating children who present with mild illnesses with MMR vaccine is a safe and efficacious practice. These results support recommendations of the Advisory Committee on Immunization Practices and the American Academy of Pediatrics.

(In conversations with epidemiologists, a disease like autism (post vaccinal encephalopathy), which may occur in 1:200 to 1:10,000 doses would require something on the order of 400,000 children in order to get adequate statistical analysis. That makes this study of 386 children meaningless for our purposes. I present it to make the point. However, there were about 2% more infections in the MMR group, which may be important in the post-vaccine disorders.)

Pathogenesis of measles virus infection: an hypothesis for altered immune responses.

J Infect Dis 1994 Nov;170 Suppl 1:S24-31

Griffin DE, Ward BJ, Esolen LM. Johns Hopkins University School of Medicine

Measles virus causes a severe systemic illness. The rash occurs simultaneously with the onset of the effector phase of the antiviral immune response and substantial evidence of immune activation. **This immune response is effective in clearing virus and in establishing long-term resistance to reinfection but is associated with immune suppression, autoimmune encephalomyelitis, and increased susceptibility to secondary infections.** This apparent paradox may be explained in part by preferential long-term activation of type 2 CD4+ T cells by measles virus infection. Preferential stimulation of type 1 CD4+ T cells by inactivated virus vaccines is hypothesized to play a role in subsequent development of atypical measles.

(I think it is critical to understand that despite 30 plus years of measles vaccine use, medical science was still guessing about the role of the virus in altering the immune response as recently as 1994 – the year my son was born. But this is also important to document that by 1994 we also knew measles caused immune suppression and autoimmune encephalomyelitis. It causes secondary infections. These seem to be inadequately dealt with in the present vaccine injury table.)

Measles virus-induced immunosuppression in vitro is associated with deregulation of G1 cell cycle control proteins.

J Gen Virol 1999 Jul;80 (Pt 7):1599-608

Engelking O, Fedorov LM, Lilischkis R, ter Meulen V, Schneider-Schaulies S.

Institut fur Virologie, University of Wurzburg, Germany.

Langerhans cells are susceptible to measles virus infection and actively suppress T cell proliferation.

Eur J Dermatol 1998 Sep;8(6):413-20

Steineur MP, Grosjean I, Bella C, Kaiserlian D.

INSERM U. 404 "Immunite et Vaccination", Bat. Pasteur, av. Tony-Garnier, 69365 Lyon Cedex 07, France.

Measles virus infects human dendritic cells and blocks their allostimulatory properties for CD4+ T cells.

J Exp Med 1997 Sep 15;186(6):801-12

Grosjean I, Caux C, Bella C, Berger I, Wild F, Banchereau J, Kaiserlian D.

Institut National de la Sante et de la Recherche Medicale U 404 "Immunite et Vaccination," Lyon, France

Induction of maturation of human blood dendritic cell precursors by measles virus is associated with immunosuppression.

Proc Natl Acad Sci U S A 1997 May 13;94(10):5326-31

Schnorr JJ, Xanthakos S, Keikavoussi P, Kampgen E, ter Meulen V, Schneider-Schaulies S.

Institute for Virology and Immunobiology of the University of Wurzburg, Versbacher Strasse 7, D-97078 Wurzburg, Germany.

Infection of human dendritic cells by measles virus induces immune suppression.
Adv Exp Med Biol 1997;417:421-3
Kaiserlian D, Grosjean I, Caux C.
INSERM Unit 404, Immunite et Vaccination, Institut Pasteur de Lyon, France.

Interaction of measles virus glycoproteins with the surface of uninfected peripheral blood lymphocytes induces immunosuppression in vitro.
Proc Natl Acad Sci U S A 1996 Nov 12;93(23):13194-9
Schlender J, Schnorr JJ, Spielhoffer P, Cathomen T, Cattaneo R, Billeter MA, ter Meulen V, Schneider-Schaulies S.
Institute for Virology and Immunobiology, University of Wurzburg, Germany.

CD46, a complement regulatory protein/measles virus receptor, and its relation to hematological disorders.
Int J Hematol 1996 Aug;64(2):101-9
Seya T.
Interitance and Variation' in PRESTO, Research Development Cooperation of Japan (JRDC), Kyoto, Japan.

Articles related to Anerobic Infection and Autism

Short-term benefit from oral vancomycin treatment of regressive-onset autism.
J Child Neurol 2000 Jul;15(7):429-35
Sandler RH, Finegold SM, Bolte ER, Buchanan CP, Maxwell AP, Vaisanen ML, Nelson MN, Wexler HM.

Autism and Clostridium tetani.
Med Hypotheses 1998 Aug;51(2):133-44
Bolte ER.

Thimerosal Related Articles

Impact of Recommendations to Suspend the Birth Dose of Hepatitis B Virus Vaccine.
JAMA 2001 Apr 11;285(14):1874-1879
Oram RJ, Daum RS, Seal JB, Lauderdale DS.

University of Chicago, 5841 S Maryland Ave, MC 6054, Chicago, IL 60637.

roram@peds.bsd.uchicago.edu

CONTEXT: In July 1999, due to concerns about thimerosal content, the American Academy of Pediatrics (AAP) and the Public Health Service (PHS) recommended suspending hepatitis B virus (HBV) vaccination at birth except for mothers who had positive or unknown hepatitis B surface antigen (HBsAg) status. In September 1999, the Centers for Disease Control and Prevention recommended that hospitals resume HBV vaccination at birth with a new thimerosal-free vaccine. Whether the 2 changes in recommendations within 3 months led to less-than-optimal compliance in hospital nurseries is unknown. OBJECTIVE: To determine hospital HBV vaccination policy before the recommendation for delay of HBV vaccination and 1 year later. DESIGN, SETTING, AND PARTICIPANTS: Survey of all 46 hospitals with obstetric services and neonatal nurseries in Cook County, Illinois. MAIN OUTCOME MEASURES: Hepatitis B virus immunization practices before July 1999 and in August 2000; hospital factors associated with routine HBV immunization and compliance with AAP and PHS recommendations. RESULTS: Before July 1999, 74% of surveyed hospital nurseries offered HBV vaccine to all neonates; only 39% did so in August 2000. Being located in the Chicago city limits (88% vs 57%; P =.02) and having an academic affiliation (93% vs 66%; P =.05) were positively associated with routine neonatal immunization before July 1999. Both academic affiliation and city location were associated with routine immunization in August 2000 (71% vs 25% [P =.003] and 60% vs 14% [P =.002], respectively) and with compliance with recommendations for suspension (57% vs 25% [P =.03] and 56% vs 10% [P =.001]). CONCLUSIONS: We documented a 35% decrease in hospital nurseries that routinely offered HBV immunization 1 year after the AAP and PHS recommendations were made. Special efforts may be required to make at-birth administration of HBV vaccination universal.

(We must deal with the reality that our vaccine policy exposed a generation of newborns to a neurotoxin – thimerosal. At birth HBV is a completely unwarranted policy that must be rethought.- regardless of mercury considerations.)

Limiting Infant Exposure to Thimerosal in Vaccines and Other Sources of Mercury

Neal A. Halsey, MD

***JAMA* Vol. 282 No. 18, November 10, 1999**

Excerpted: **Based on the limited data available, experts have concluded that the toxicity of ethylmercury may be similar to methylmercury**. Data from 2 recent studies examining the relationship between methylmercury exposure and neuropsychological outcome in children suggest that intermittent large exposures may pose more risk than small daily doses. Faeroese children at age 7 years who had been exposed in utero to intermittent bolus doses of methylmercury were found to have subtle neurologic impairments based on domain-specific neuropsychological testing.The total exposures during pregnancy were in the range that was not associated with impairments by global IQ testing in Seychelloises children aged 5.5 years who had been exposed to smaller daily doses.

Regulation of sodium currents through oxidation and reduction of thiol residues.

Neuroscience 2000;101(1):229-36
Evans JR, Bielefeldt K.

University of Iowa, 4614 JCP, 200 Hawkins Drive, Iowa City, IA 52242, USA.

Changes in redox state are involved in several physiological and pathophysiological processes. Previous experiments have demonstrated that nitric oxide can function as a reactive oxygen species, inhibiting neuronal sodium currents by nitrosylation of thiol residues. We hypothesized that nitric oxide and thiol oxidizers similarly modulate voltage-dependent sodium currents. Voltage-dependent sodium currents were studied with the whole-cell patch-clamp technique in NB41A3 neuroblastoma cells. The nitric oxide donor 3-(2-hydroxy-2-nitroso-1-propylhydrazino)-1-propanamine did not affect sodium currents. **In contrast, the thiol oxidizers thimerosal and 4,4'-dithiopyridine significantly inhibited sodium currents. The effect of thimerosal persisted after washout, but could be fully reversed by the reducing agent dithiothreitol. Reduced glutathione did not restore the sodium current amplitude when given extracellularly, while intracellular glutathione prevented the inhibitory effect of thimerosal.** These results demonstrate that the oxidation and reduction of thiol residues alters the properties of voltage-sensitive sodium channels and may play an important role in the regulation of membrane excitability.

(I think this is important in its relationship to potential neurological symptoms. It also speaks to the fact that thimerosal itself can cause symptoms without converting to ethylmercury.)

Thiomersal as a vaccine preservative.

Wkly Epidemiol Rec 2000 Jan 14;75(2):12-6

Thiomersal poses a theoretical low risk of neurodevelopmental toxicity in infants. The known risk of morbidity and mortality from vaccine-preventable diseases and of contaminated multidose vaccine vials far outweigh any potential risk posed by thiomersal. However, with the weight of public opinion against the use of mercury of any sort, WHO and other agencies have begun the process of reducing and removing thiomersal from vaccines. In the short term (the next 3 years), modifications to existing strategies will result in a reduction in exposure to thiomersal. Over the long term (beyond 3 years), efforts will be focused on new vaccine-delivery technologies, alternative preservatives and combination vaccines, further reducing and eventually, perhaps, eliminating thiomersal from vaccines.

(But of course mulitdose vials are not a requirement except from an economic perspective.)

Thimerosal induces toxic reactions.

Int Arch Allergy Immunol 1994 Dec;105(4):408
Wantke F, Hemmer W, Gotz M, Jarisch R

Thimerosal induces toxic reaction in non-sensitized animals.

Int Arch Allergy Immunol 1994 Jul;104(3):296-301
Uchida T, Naito S, Kato H, Hatano I, Harashima A, Terada Y, Ohkawa T, Chino F, Eto K.

Department of Safety Research on Biologics, National Institute of Health, Tokyo, Japan.

The effects of injection of thimerosal solution on nonsensitized animals was investigated. Intrafootpad injection of thimerosal solution in nonsensitized mice resulted in a swelling response which peaked 1 h after injection and lasted for more than 24 h. Histopathological examination showed that there were severe edema and infiltration of polymorphonuclear neutrophils at the site of injection. An increased vascular permeability was observed after cutaneous injection of thimerosal solution on the back of nonsensitized rats. Since mercuric chloride and methyl mercury induced severer reactions, and thiosalicylic acid had no effect, mercury contained in thimerosal would have caused the reactions observed in this study. **These results suggest that part of these hypersensitivity reactions against thimerosal observed among patients were possibly induced by the toxic effect of thimerosal. Therefore, thimerosal contained as a preservative in vaccine may augment the side-effects of the vaccination.**

(By 1994, the year my son was born, thimerosal was known to be a problem in vaccines – no public warning was issued by any public health officials in this country.)

Ethylmercuric chloride: the responsible agent in thimerosal hypersensitivity.

Contact Dermatitis 1993 Sep;29(3):152-4
Pirker C, Moslinger T, Wantke F, Gotz M, Jarisch R.

Dermatologic and Pediatric Allergy Clinic, Vienna, Austria.

The causative agent of thimerosal allergy (sodium ethylmercury thiosalicylate) has not previously been thoroughly investigated. To evaluate whether the organic mercury component or the thiosalicylic acid molecule induces thimerosal sensitization, 23 patients positive to thimerosal were patch tested with ethylmercuric chloride, thiosalicylic acid and 8 different derivatives of mercury. To date, ethylmercuric chloride has not been tested in thimerosal allergy. 19/23 patients (82%) showed positive patch test reactions to ethylmercuric chloride. 4/23 patients negative to ethylmercuric chloride reacted positively to thimerosal 0.1% but not to thimerosal 0.05%. 8/23 patients (35%) also reacted to other mercurials. 20 controls negative to thimerosal showed negative patch test

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reactions to ethylmercuric chloride. Neither patients nor controls reacted to thiosalicylic acid. **These results indicate that testing with thimerosal 0.1% leads to false-positive reactions and that the ethyl mercury component is the responsible agent in thimerosal allergy.**

(It seems amazing that by 1993 there was little research on this widely used vaccine constituent.)

Hypersensitivity to thiomersal in hepatitis B vaccine.

Lancet 1991 Sep 14;338(8768):705
Noel I, Galloway A, Ive FA.

The case against thiomersal.

Lancet 1991 Aug 3;338(8762):315-6
Seal D, Ficker L, Wright P, Andrews V.

Articles related to Measles and Endothelial Infection & Disruption

Brain endothelial cell infection in children with acute fatal measles.

J Clin Invest 1995 Nov;96(5):2478-81
Esolen LM, Takahashi K, Johnson RT, Vaisberg A, Moench TR, Wesselingh SL, Griffin DE

Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA.

Neurologic diseases are important complications of measles. The role of virus infection of the central nervous system as well as the route of virus entry has been unclear. Five autopsied cases of individuals who died with severe acute measles 3-10 d after the onset of the rash were studied for evidence of viral involvement of the central nervous system. In all cases, in situ hybridization and RT-PCR in situ hybridization techniques showed endothelial cell infection. Immunoperoxidase staining with an anti-ferritin antibody revealed a reactive microgliosis. **These data suggest that endothelial cells in the brain are frequently infected during acute fatal measles.** This site of infection may provide a portal of entry for virus in individuals who subsequently develop subacute sclerosing panencephalitis or measles inclusion body encephalitis and a target for immunologic reactions in post-measles encephalomyelitis.

Measles virus infection of cerebral endothelial cells and effect on their adhesive properties.

Vet Microbiol 1995 May;44(2-4):135-9
Cosby SL, Brankin B
Division of Molecular Biology, School of Biology and Biochemistry, Queen's University of Belfast, UK.

Measles virus (MV) RNA is present in endothelial cells (Ec) in brain tissue from cases of subacute sclerosing panencephalitis (SSPE) and relatively high titres of infectious virus are produced in human cerebral Ec in vitro. Infection of Ec at the blood-brain barrier could therefore provide the opportunity for entry of virus to the CNS. Adhesion of syngeneic splenocytes to MV infected murine (Balb/c) cerebral Ec is found to be upregulated. **Increased expression of endothelial adhesion molecules, following virus infection at the blood-brain-barrier, may be an important mechanism in inducing inflammatory infiltration of the CNS in SSPE.**

(I believe this is likely part of the explanation of the anti-Endothelial anti-brain antibodies observed by Anne, Connolly, et al, J Peds May 1999. It is also a likely part of why elevated Lipoprotein(a) could be an additive or compounding feature of the MMR injury pattern. Lp(a) is a sticky fatty protein that would be attracted to increased endothelial cell adhesion factors.

Adhesion molecule expression and lymphocyte adhesion to cerebral endothelium: effects of measles virus and herpes simplex 1 virus.

J Neuroimmunol 1995 Jan;56(1):1-8

Brankin B, Hart MN, Cosby SL, Fabry Z, Allen IV

Measles virus induction of human endothelial cell tissue factor procoagulant activity in vitro.

J Gen Virol 1994 Nov;75 (Pt 11):286[illegible]-71

Mazure G, Grundy JE, Nygard G, Hudson M, Khan K, Srai K, Dhillon AP, Pounder RE, Wakefield AJ

Inflammatory Bowel Disease Study Group, Royal Free Hospital School of Medicine, London, U.K.

Measles virus infection of microvascular endothelium in vivo and ensuing endothelial cell activation may be important in the pathogenesis of subsequent inflammation in target organs. This study investigated the capacity of measles virus to induce procoagulant activity, in vitro, in endothelial cells isolated from human umbilical cord veins. Endothelial cells were infected with a clinical isolate of measles virus propagated in Vero cells. Cells were also incubated with bacterial lipopolysaccharide (10 micrograms/ml), herpes simplex virus type 1, cytomegalovirus or culture medium alone as positive and negative controls, respectively. **Endothelial cell procoagulant activity was measured in a one-stage clotting assay. Measles virus stimulated both a time and dose-dependent endothelial cell procoagulant response by the induction of tissue factor synthesis, confirmed by both immunocytochemistry and its dependence on factor VII for activity.** This activity was reduced by u.v.-irradiation of the virus. Infected cells were analysed by double immunofluorescent staining for both tissue factor and measles virus N-protein, and examined using confocal scanning laser microscopy. Cells expressing tissue factor were also positive for the measles virus N-protein. Low levels of interleukin-1 were detected in some viral inocula derived from measles virus-infected Vero cells, however neutralising antibody to interleukin-1 failed to inhibit the endothelial cell procoagulant response to measles virus, whereas it significantly reduced procoagulant activity induced in endothelial cells by recombinant interleukin-1. **The capacity of measles virus to induce endothelial tissue factor in vitro, may be relevant to the thrombotic vasculopathy associated with measles virus infection in vivo.**

(This is what appears to be happening in the Thrombophilia related post MMR groups of children we describe. In addition, those children who eventually become symptomatic to MMR infection may be that population with either genetic thrombophilia factors (Leiden V, Lp(a), Factor II defects, etc) or with induced thrombophilia secondary to other factors.

The pathogenesis of Crohn's disease.

J Gastroenterol 1994 Jul;29 Suppl 7:11-5

Pounder RE

University Department of Medicine, Royal Free Hospital School of Medicine, London, UK.

This paper describes a program of research undertaken by the Inflammatory Bowel Disease Study Group at the Royal Free Hospital School of Medicine. The Group has tested the hypothesis that the primary pathological abnormality in Crohn's disease is in the mesenteric blood supply. The first experiments involved microcorrosion resin casting of the arterial supply of specimens of resected intestine affected by Crohn's disease. This revealed severe damage to submucosal blood vessels, even in areas that were not affected macroscopically by Crohn's disease. Resected specimens of bowel were examined after perfusion-fixation: 85% of granulomas were associated with blood vessels, demonstrating that Crohn's disease is a granulomatous vasculitis. **Patients with Crohn's disease usually have one or more features of a hypercoagulable state, which may increase the risk of ischemic damage.** A model of Crohn's disease was developed in the ferret intestine, by embolizing mesenteric blood vessels using latex particles. Acute embolization results in patchy necrosis of the mucosa, with subsequent recovery. Surgical incision and anastomosis in a previously embolized area results in intense ulceration--suggesting that recurrent Crohn's disease after surgery is due to a second ischemic insult to an already damaged intestine. Finally, electron microscope studies have investigated the mesenteric vascular endothelium associated with granulomata in Crohn's disease. **Viral particles have been identified within the vascular endothelium, with the appearance of paramyxoviridae. In situ hybridization and other studies suggest that these particles are measles virus.**

Cerebral endothelial cell infection by measles virus in subacute sclerosing panencephalitis: ultrastructural and in situ hybridization evidence.

Neuropathol Appl Neurobiol 1991 Aug;17(4):289-97

Kirk J, Zhou AL, McQuaid S, Cosby SL, Allen IV

Multiple Sclerosis Research Laboratory, Queen's University of Belfast.

Infection of vascular endothelium plays a central role in the pathogenesis of acute measles virus infection outside the central nervous system (CNS) but has not been described in the human CNS. An ultrastructural survey was made of blood vessels in five cases of subacute sclerosing panencephalitis (SSPE) to determine whether or not infection of cerebral vascular endothelium occurred in this persistent fatal CNS disease caused by measles virus. Morbillivirus nucleocapsids were found in a few endothelial cells in three necropsy cases but not in the limited tissue available from two biopsies. In a severe parenchymal lesion in one necropsied case, endothelial cells hybridized in situ with a biotinylated probe specific for the N genomic RNA of measles virus. **It is concluded that human cerebral endothelium is susceptible to measles virus infection.**

(I believe this factor may be core to the perfusion, autoimmunity and thrombophilia related findings.)

Influence of the measles virus on the proliferation and protein synthesis of aortic endothelial and smooth muscle cells.

Acta Microbiol Hung 1990;37(2):193-200

Csonka E, Bayer PI, Buki K, Varady G

Second Department of Pathology, Semmelweis University Medical School, Budapest, Hungary.

To clarify whether some viruses could influence the different functions and membrane permeability of the aortic cells, we have examined in a model experiment the in vitro effect of the measles virus on the aortic endothelial and smooth muscle cells. The aortic cells infected with the virus failed to reveal gross cytopathic effect. Occasionally, however, syncytium formation and nuclear inclusions were observed. In infected endothelial cells lysosome containing viral nucleocapsids were seen. The early phase of measles virus replication inhibited the proliferation of endothelial cells of all species tested, while uniformly stimulated the replication of the smooth muscle cells relative to the control. In bovine aortic endothelial and smooth muscle cells the protein synthesis had been suppressed by the 4th to 6th hours postinfection. **The results indicate that measles virus infection may be among the risk factors of atherosclerosis. It may damage endothelial cells by altering the cell membrane permeability and could induce proliferation of aortic smooth muscle cells.**

(This pattern of thinking has occurred to various researchers worldwide, and in Dr. Wakefield's defense, none of them have an interest in establishing a link between vaccines and autism, based on any of their published works.

Measles rash. I. Light and electron microscopic study of skin eruptions.

Arch Virol 1975;47(4):295-307
Kimura A, Tosaka K, Nakao T

Measles skin lesions were studied by light and electron microscopy. In the epidermis multinucleated giant cells were observed just beneath the hypertrophic horney layer at the maximum stage of rash; they were believed to result by an abnormal process of hyper- or parakeratosis. Neither typical inclusions nor viral nucleocapsids could be detected in any part of the epidermal layer. Most characteristical changes were dermal edema and spongiosis with mononuclear cell infiltration as well as **the detection of measle virus-like microtubular structures (nucleocapsids) in the endothelium of dermal capillaries. Is is assumed that measles exanthema is a manifestation of an Arthus reaction elicited by viral antigen in the endothelium of dermal capillaries.**

(So, as early as 1975, it became apparent that endothelial infection was core to the measles course of infection. I think this is a consistently documented finding in our literature and given our findings and those of others regarding perfusion and coagulation abnormalities in autism or past-vaccinal encephalopathy, should cause us serious concern when discussing vaccine safety.)

Virus infection of endothelial cells.

J Infect Dis 1981 Feb;143(2):266-73**Friedman HM, Macarak EJ, MacGregor RR, Wolfe J, Kefalides NA**

Endothelial injury is important in the pathogenesis of thrombosis, atherosclerosis, disseminated intravascular coagulation, and vasculitis. The ability of several common human viruses to infect cultures of endothelial cells obtained from human umbilical veins or bovine thoracic aorta was demonstrated. Indicators of infection included cytopathology, viral growth curves, and antigen detection by immunofluorescence. Herpes simplex virus type 1, adenovirus type 7, measles virus, and parainfluenza virus type 3 infected both human venous and bovine aorta endothelium. Mumps virus, poliovirus type 1, and echovirus type 9 grew only in human venous cells; coxsackievirus B4 infected only bovine arterial cultures; and cytomegalovirus, influenza A/Victoria/75 (H3N2) virus, and respiratory syncytial virus failed to grow in either cell culture. During replication some viruses caused acute lytic changes; some produced chronic, less destructive alterations; and other induced no apparent cytopathology. **The results suggest that viral replication within endothelium may be important in the pathogenesis of viral disease of initiation of vessel-wall injury.**

An increased factor VIII antigen as an indicator of endothelial damage in measles.

Thromb Res 1979;14(4-5):805-10
Corda R, Alberti M, Caocci L, Putzolu G, Mannucci PM

An immunofluorescent and electron microscopic study of measles skin eruptions.

Tohoku J Exp Med 1975 Nov;117(3):245-56
Kimura A, Tosaka K, Nakao T

Immunofluorescent study was attempted to determine whether or not virus antigen were present in the epidermis of measles eruptions. The electron microscopic observations of the same materials were also performed to detect viral localization in affected skins. The failure to detect any virus antigen in affected eipdermis throughout all eruptive stages seems to be sufficient evidence to conclude that measles rash is not a manifestation of viral replication in the epidermis. Dotted fluorescences were detected in a specimen taken at pre-eruptive day in capillary endothelium of dermis. At the same stage, microtubular structures which were probably identical with measles virus nucleocapsids occurred in capillary endothelium under the electron microscopic observations. It is concluded that measles rash is possibly caused by an antigen-antibody reaction of Arthus type. On very rare occasions, measles virus nucleocaspids were found in the cytoplasm of dermal fibroblast in the vicinity of dermal capillary. Ultrastructural features of these nucleocapsids were demonstrated to be identical to features of microtubular structures found in endothelial cells.

Pathogenesis of viral encephalitis: demonstration of viral antigen(s) in the brain endothelium.

Acta Neuropathol (Berl) 1983;60(1-2):107-12
Wisniewski HM, Brown HR, Thormar H

One of the enigmas in the pathogenesis of inflammation is why the white cells adhere to the endothelium. In trying to define the pathogenic mechanism, we carried out experiments on ferrets infected with an SSPE strain of measles virus. **Using immunoperoxidase labeling techniques, viral antigens were demonstrated on the luminal surface and in the cytoplasm of endothelial cells, irrespective of the presence or absence of inflammatory changes. The degree of inflammation corresponded well with antibody titer. These data suggest that the viral antigen in the endothelial cells is the site of interaction between these cells and sensitized lymphoid cells.**

Articles related to Mercury and Endothelial Disruption

Epidemics of vascular toxicity and pulmonary hypertension: what can be learned?

J Intern Med 2000 Jan;247(1):11-7
Egermayer P

Canterbury Respiratory Research Group, Christchurch, New Zealand.
crrg@chmeds.ac.nz

Epidemics of vascular disease caused by toxins and infectious agents affecting both humans and animals have been common in history. Examples of agents implicated include anorexients, ergotamine, mercury, arsenic, vinyl chloride, thorotrast, plant alkaloids, nitrites, toxic oil, tryptophan and bacterial, viral and parasitic infections. A major characteristic of these disorders is endothelial dysfunction, which may manifest itself in vasospastic disorders, sclerodermiform skin lesions, fibrosis, osteolytic lesions, polyneuropathy and portal and pulmonary hypertension. Angiosarcoma may also be a late outcome. These diseases are more common than is generally appreciated. The aetiology is usually multifactorial. This and other factors contribute to delayed recognition.

Effects of lead and mercury on histamine uptake by glial and endothelial cells.

Pharmacol Toxicol 1995 Jun;76(6):339-42
Huszti Z, Balogh I

Department of Pharmacodynamics, Semmelweis University of Medicine, Budapest, Hungary.

The effects of lead and mercury on [3H]-histamine uptake by cultured astroglial and endothelial cells of rat brain were studied. Experimental data showed that both metal ions inhibited the uptake in both cell types of concentrations as low as 1-10 microM. The effects were consistent with non/competitive inhibitions. With either lead or mercury exposure, the inhibition of the uptake was greater in astroglial than in cerebral endothelial cells. Contrary to the above findings, 100 microM of mercuric chloride produced stimulation of histamine uptake and this stimulation was much more pronounced in cultured cerebral endothelial cells than in astroglial cells. Inhibition of [3H]-histamine uptake by lead acetate and mercuric chloride was considered to be association with a loss of the transmembrane Na+ and/or K+ gradient while stimulation of the uptake by high concentration of mercury might be related to a direct effect on histamine transporter. It is noteworthy, that cultured astroglial cells, derived from neonatal rat brain, are much more sensitive to the toxic effects of these heavy metal ions than cultured endothelial cells derived from the brain capillaries of the same species of animals.

The early effects of methylmercury on the developing rat brain.

Acta Neuropathol (Berl) 1990;80(4):432-8
Geelen JA, Dormans JA, Verhoef A

Department of Teratology, National Institute of Public Health and Environmental Protection, Bilthoven, The Netherlands.

The effects of organic mercury compounds on the development of the brain are well known since the exposure of people at a large scale to methylmercury in the Minamata Bay area and in Iraq. The neuropathological examination of the brains of children prenatally exposed revealed dysplasia of the cerebral and cerebellar cortex, neuronal ectopia and several other developmental disturbances. In this experimental study we examined developmental mechanisms involved in methylmercury-induced cerebral anomalies. By examining the fetuses soon after treatment we concentrated in the initial effects of the treatment. The pregnant rats were given 10 mg/kg methylmercury chloride i.p. on day 18. **Already at 2 h after administration mitochondrial degeneration occurred in the endothelium of the cerebral capillaries.** Subsequently hemorrhages developed interfering with the cellular arrangement in the ventricular zone, with neuronal migration in the intermediate zone and with the development of the cortical cytoarchitecture. Macrophages and cavities appeared in the hemorrhagic areas. **It is suggested that the abnormalities seen in the experiments can be considered as the initial methylmercury-induced effects which, in combination with various other toxic effects, ultimately result in the anomalies that have been observed in the brains of children prenatally exposed to methylmercury.**

Alterations of thiol metabolism in human cell lines induced by low amounts of copper, mercury or cadmium ions.

Toxicology 1998 Apr 3;126(3):203-12

Hultberg B, Andersson A, Isaksson A

Department of Clinical Chemistry, University Hospital, Lund, Sweden.

Ions of metals such as mercury, cadmium and copper are known to exhibit a high affinity for thiol groups and may therefore severely disturb many metabolic functions in the cell. The aim of the present study was to identify the most sensitive changes of thiol metabolism induced by the addition of low concentrations of metal ions in order to elucidate the mechanisms of metal-toxicity. The effects on thiol metabolism by copper ions seemed to differ from that of mercury and cadmium ions. Copper ions exhibited mainly two effects that were different from those of mercury and cadmium ions. They lowered the reduced fractions of thiols and increased the release of homocysteine into the medium, whereas mercury and cadmium ions mainly influenced the metabolism of glutathione by increasing its synthesis. Even 0.1 micromol/l of copper ions increased the release of homocysteine in HeLa cell lines. An increased cellular concentration of glutathione and an increased release of glutathione into the medium were observed after addition of mercury and cadmium ions at a concentration of 1 micromol/l, which is just above the toxicity limit in human blood. The different cell lines varied in some respects in their response to the addition of metal ions. Cadmium ions had no effect on thiol metabolism in endothelial cell lines, and copper ions did not significantly increase the release of homocysteine into the medium in hepatoma cell lines. Furthermore, the metabolism of thiols during basal conditions (without the addition of metal ions) differed somewhat in the three cell lines investigated. One example is the low amount of extracellular glutathione in hepatoma cell lines, which probably was due to its rapid degradation to cysteinylglycine by gamma-glutamyl-transpeptidase.

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Mercury-stimulated histamine uptake and binding in cultured astroglial and cerebral endothelial cells.

J Neurosci Res 1997 Apr 1;48(1):71-81
Huszti Z, Madarasz E, Schlett K, Joo F, Szabo A, Deli M

Department of Pharmacodynamics, Semmelweis University of Medicine, Budapest, Hungary.

The effects of mercuric compounds on histamine uptake and binding to uptake carrier in cultured rat astroglial and cerebral endothelial cells were investigated. Experimental results showed that mercuric compounds produced strong stimulation of glial and cerebroendothelial histamine uptake over a concentration range of 25-500 microM. The stimulated histamine uptake showed characteristics similar to those described for basal uptake in terms of sensitivity to inhibitory agents (e.g., impromidine) and the requirement of external Na+. Mercury-induced stimulation of histamine uptake could be abolished by sulfhydryl agents, dithiotreitol and cysteamine, indicating a complete reversal of, and not simply a protection from, the action of mercury. Basal and stimulated uptake of histamine represent bindings to uptake carrier with high and closely equal affinities but markedly higher capacities for stimulated uptake. In controls, the mean value of apparent KD (derived from saturation kinetics at equilibrium) was obtained as 26.7 +/- 3.9 nM for astroglial cells; and 100 microM mercuric chloride did not modify it significantly. In contrast, the apparent Bmax values differed markedly; found as 0.63 +/- 0.10 pmol/mg protein and 3.32 +/- 0.47 pmol/mg protein in the absence and the presence of 100 microM mercuric chloride respectively. For the cerebral endothelial cell line, RBE4, the apparent KD was calculated as 22.5 +/- 3.2 nM and was comparable to that obtained for astroglial cells in control and mercury-stimulated conditions. The apparent Bmax values were less, but markedly different in these conditions, obtained as 0.18 +/- 0.03 pmol/mg protein and 1.2 +/- 0.36 pmol/mg protein in the absence and the presence of mercuric ion respectively. In both cells, impromidine, the potent inhibitor of basal and stimulated histamine uptake, decreased the enhanced capacities of histamine binding (Bmax) (without affecting the dissociation constant, KD) in micromolar range, comparable to its inhibiting potency. Results confirmed that mercuric ion might enhance the binding capacity of histamine carrier and protein sulfhydryls might play a role in this effect. The observed stimulations by mercuric compounds suggest close similarities in the mechanism of histamine uptake and the structure of histamine carrier in astroglial and cerebral endothelial cells.

Inhibitory effect of lead on the repair of wounded monolayers of cultured vascular endothelial cells.

Toxicology 1997 Feb 28;117(2-3):193-8
Fujiwara Y, Kaji T, Sakurai S, Sakamoto M, Kozuka H
Department of Environmental Science, Faculty of Pharmaceutical Sciences, Hokuriku University, Kanazawa, Japan.

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We investigated the effect of lead nitrate (0.5-5.0 microM) on the repair of wounded monolayer of cultured bovine aortic endothelial cells. It was morphologically found that lead decreases the appearance of the cells in the wounded area in a concentration-dependent manner without degenerative changes after a 48-h incubation. Although mercury weakly inhibited the repair with nonspecific cell damage, the other cations including bismuth, cobalt, manganese and nickel failed to affect the repair. The inhibition of endothelial repair caused by lead was observed even when stimulated by exogenous either basic or fibroblast growth factor. **These results indicated that inhibition of the repair process of damaged endothelial cell layer is a component of lead-induced vascular lesions such as atherosclerosis.**

Articles related to Coagulation and Autoimmune Disease

Endothelial cell autoantibodies are a marker of disease susceptibility in inflammatory bowel disease but apparently not linked to persistent measles virus infection.

Clin Immunol 2000 Jun;95(3):197-202

Folwaczny C, Loeschke K, Schnettler D, Jager G, Wiebecke B, Hoelscher M, Sauer T, Konig A, Endres SP, Fricke H.

(This study did not find measles virus, but as well know unless you can detect less than 1000 copies of the virus you will miss the virus – their technology would not have allowed for this level of detection).

Evidence for activation of coagulation in Crohn's disease.

Blood Coagul Fibrinolysis 1992 Dec;3(6):773-8

Hudson M, Hutton RA, Wakefield AJ, Sawyerr AM, Pounder RE.

University Department of Medicine, Royal Free Hospital and School of Medicine, London, UK.

Haemostatic changes in 16 patients with Crohn's disease were studied from active disease into clinical remission and beyond. Elevated concentrations of fibrinopeptide A (FpA) and prothrombin fragments F1 + 2 (F1 + 2) were found at times of both active (FpA median 3.2, range [0.3-40] ng/ml and F1 + 2 median 2.3, range [0.3-18] nm/l) and inactive disease (FpA median 2, range [0.4-40] ng/ml and F1 + 2 median 1.3, range [0.2-20) nm/l]. We also measured the physiological inhibitors of coagulation and fibrinolysis; there was no significant difference in the levels of antithrombin III, protein C or the Exner ratio between active and inactive disease. Free protein S levels were significantly lower in active disease (median 34, range 9-54 U/dl) than in remission (median 40, range 12-65 U/dl). Plasminogen activator inhibitor type 1 (PAI-1) was significantly raised in

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remission (median 11, range 3-32 ng/ml) when compared to active disease (median 7, range 3-42 ng/ml). The D-dimer correlated significantly with fibrinopeptide A ($P < 0.001$), suggesting reactive fibrinolysis in some patients. Most (35/52, 67%) samples showed evidence of persistent haemostatic activation (elevated FpA and/or F1 + 2) during phases of apparent clinical remission in Crohn's disease, a factor that is not reflected by clinical activity scores. **This study supports the hypothesis that coagulation is activated in the mesenteric vasculature of patients with Crohn's disease.**

Anti-phospholipid antibodies in the mercuric chloride treated brown Norway rat.

J Autoimmun 1994 Aug;7(4):457-67
Marriott JB, Qasim F, Oliveira DB.

Activation and control of complement, inflammation, and infection associated with the use of biomedical polymers.

ASAIO J 2000 Nov-Dec;46(6):S53-62
Janatova J.

Immunobiology of human vascular endothelium.

Immunol Res 1999;19(2-3):225-32
Pober JS.

Biology of endothelium.

Lupus 1998;7 Suppl 2:S41-3
Maruyama I.

Association of maternal endothelial dysfunction with preeclampsia.

JAMA 2001 Mar 28;285(12):1607-12
Chambers JC, Fusi L, Malik IS, Haskard DO, De Swiet M, Kooner JS.

Articles related to Abnormal Cerebral Blood Flow in Autism

The functional neuroanatomy of social behaviour: changes in cerebral blood flow when people with autistic disorder process facial expressions.

Brain. 2000 Nov;123 (Pt 11):2203-12.
Critchley HD, Daly EM, Bullmore ET, Williams SC, Van Amelsvoort T, Robertson DM, Rowe A, Phillips M, McAlonan G, Howlin P, Murphy DG.

Functional neuroimaging of autistic disorders.
Rumsey JM, Ernst M.
Ment Retard Dev Disabil Res Rev. 2000;6(3):171-9. Review.

Abnormal regional cerebral blood flow in childhood autism.
Ohnishi T, Matsuda H, Hashimoto T, Kunihiro T, Nishikawa M, Uema T, Sasaki M.
Brain. 2000 Sep;123 (Pt 9):1838-44.

Cerebral blood flow abnormalities in adults with infantile autism.
George MS, Costa DC, Kouris K, Ring HA, Ell PJ.
J Nerv Ment Dis. 1992 Jul;180(7):413-7.

Articles related to Measles or Autism and Enterocolitis

(These are not a list of the many detractors from these observations)

Detection and sequencing of measles virus from peripheral mononuclear cells from patients with inflammatory bowel disease and autism.
Dig Dis Sci. 2000 Apr;45(4):723-9.
Kawashima H, Mori T, Kashiwagi Y, Takekuma K, Hoshika A, Wakefield A.

Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children.
Lancet 1998 Feb 28;351(9103):637-41
Wakefield AJ, Murch SH, Anthony A, Linnell J, Casson DM, Malik M, Berelowitz M, Dhillon AP, Thomson MA, Harvey P, Valentine A, Davies SE, Walker-Smith JA.

Colonic CD8 and gamma delta T-cell infiltration with epithelial damage in children with autism.
J Pediatr 2001 Mar;138(3):366-72
Furlano RI, Anthony A, Day R, Brown A, McGarvey L, Thomson MA, Davies SE, Berelowitz M, Forbes A, Wakefield AJ, Walker-Smith JA, Murch SH.

OBJECTIVES: We have reported colitis with ileal lymphoid nodular hyperplasia (LNH) in children with regressive autism. The aims of this study were to characterize this lesion and determine whether LNH is specific for autism. METHODS: Ileo-colonoscopy was performed in 21 consecutively evaluated children with autistic spectrum disorders and bowel symptoms. Blinded comparison was made with 8 children with histologically normal ileum and colon, 10 developmentally normal children with ileal LNH, 15 with Crohn's disease, and 14 with ulcerative colitis. Immunohistochemistry was performed for cell lineage and functional markers, and histochemistry was performed for glycosaminoglycans and basement membrane thickness. RESULTS: Histology

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demonstrated lymphocytic colitis in the autistic children, less severe than classical inflammatory bowel disease. However, basement membrane thickness and mucosal gamma delta cell density were significantly increased above those of all other groups including patients with inflammatory bowel disease. CD8(+) density and intraepithelial lymphocyte numbers were higher than those in the Crohn's disease, LNH, and normal control groups; and CD3 and plasma cell density and crypt proliferation were higher than those in normal and LNH control groups. Epithelial, but not lamina propria, glycosaminoglycans were disrupted. However, the epithelium was HLA-DR(-), suggesting a predominantly T(H)2 response. INTERPRETATION: Immunohistochemistry confirms a distinct lymphocytic colitis in autistic spectrum disorders in which the epithelium appears particularly affected. **This is consistent with increasing evidence for gut epithelial dysfunction in autism.**

Early measles virus infection is associated with the development of inflammatory bowel disease.

Am J Gastroenterol 2000 Jun;95(6):1480-5

Pardi DS, Tremaine WJ, Sandborn WJ, Loftus EV Jr, Poland GA, Harmsen WS, Zinsmeister AR, Melton LJ 3rd.

Department of Health Sciences Research, Mayo Clinic and Mayo Foundation, Rochester, Minnesota, USA.

(I assume the group at Mayo is not in conspiracy with the group at Royal Free so we need to take these data seriously)

Gastrointestinal abnormalities in children with autistic disorder.

J Pediatr 1999 Nov;135(5):559-63

Horvath K, Papadimitriou JC, Rabsztyn A, Drachenberg C, Tildon JT.

Department of Pediatrics, University of Maryland School of Medicine, Baltimore, USA.

OBJECTIVES: Our aim was to evaluate the structure and function of the upper gastrointestinal tract in a group of patients with autism who had gastrointestinal symptoms. STUDY DESIGN: Thirty-six children (age: 5.7 +/- 2 years, mean +/- SD) with autistic disorder underwent upper gastrointestinal endoscopy with biopsies, intestinal and pancreatic enzyme analyses, and bacterial and fungal cultures. The most frequent gastrointestinal complaints were chronic diarrhea, gaseousness, and abdominal discomfort and distension. RESULTS: Histologic examination in these 36 children revealed grade I or II reflux esophagitis in 25 (69.4%), chronic gastritis in 15, and chronic duodenitis in 24. The number of Paneth's cells in the duodenal crypts was significantly elevated in autistic children compared with non-autistic control subjects. Low intestinal carbohydrate digestive enzyme activity was reported in 21 children (58.3%), although there was no abnormality found in pancreatic function. Seventy-five percent of the autistic children (27/36) had an increased pancreatico-biliary fluid output after intravenous secretin administration. Nineteen of the 21 patients with diarrhea had significantly higher fluid output than those without diarrhea. **CONCLUSIONS: Unrecognized gastrointestinal disorders, especially reflux esophagitis and disaccharide malabsorption, may contribute to the behavioral problems of the non-**

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verbal autistic patients. The observed increase in pancreatico-biliary secretion after secretin infusion suggests an upregulation of secretin receptors in the pancreas and liver. Further studies are required to determine the possible association between the brain and gastrointestinal dysfunctions in children with autistic disorder.

Articles Related to Measles Induced Immune Deficiency & Persistent or Delayed Infection

Measles inclusion-body encephalitis caused by the vaccine strain of measles virus.

Clin Infect Dis 1999 Oct;29(4):855-61

Bitnun A, Shannon P, Durward A, Rota PA, Bellini WJ, Graham C, Wang E, Ford-Jones EL, Cox P, Becker L, Fearon M, Petric M, Tellier R.

Department of Critical Care Medicine, The Hospital for Sick Children, Toronto, Ontario, Canada.

We report a case of measles inclusion-body encephalitis (MIBE) occurring in an apparently healthy 21-month-old boy 8.5 months after measles-mumps-rubella vaccination. He had no prior evidence of immune deficiency and no history of measles exposure or clinical disease. During hospitalization, a primary immunodeficiency characterized by a profoundly depressed CD8 cell count and dysgammaglobulinemia was demonstrated. A brain biopsy revealed histopathologic features consistent with MIBE, and measles antigens were detected by immunohistochemical staining. Electron microscopy revealed inclusions characteristic of paramyxovirus nucleocapsids within neurons, oligodendroglia, and astrocytes. The presence of measles virus in the brain tissue was confirmed by reverse transcription polymerase chain reaction. **The nucleotide sequence in the nucleoprotein and fusion gene regions was identical to that of the Moraten and Schwarz vaccine strains**; the fusion gene differed from known genotype A wild-type viruses.

(This is an extraordinary study. It documents what Wakefield and others have speculated and observed. The vaccine MV does persist for a long time after the vaccine and that it can cause delayed disease.)

Immune response-mediated protection of adult but not neonatal mice from neuron-restricted measles virus infection and central nervous system disease.

J Virol 1999 Mar;73(3):1795-801

Lawrence DM, Vaughn MM, Belman AR, Cole JS, Rall GF.

Vitamin A, immunity, and infection.

Clin Infect Dis 1994 Sep;19(3):489-99
Semba RD.

Aberrant IgG subclass distribution to measles in healthy seropositive individuals, in patients with SSPE and in immunoglobulin-deficient patients.
Clin Exp Immunol 1990 May;80(2):202-5
Mathiesen T, Hammarstrom L, Fridell E, Linde A, Wirsen G, Smith CI, Norrby E, Wahren B.

Disease model: dissecting the pathogenesis of the measles virus.
Trends Mol Med 2001 Feb;7(2):85-8
Patterson JB, Manchester M, Oldstone MB.

Cell membrane-associated measles virus components inhibit antigen processing.
Virology 2001 Jan 20;279(2):422-8
Marttila J, Hinkkanen A, Ziegler T, Vainionpaa R, Salmi A, Ilonen J.

Consequences of Fas-mediated human dendritic cell apoptosis induced by measles virus.
J Virol 2000 May;74(9):4387-93
Servet-Delprat C, Vidalain PO, Azocar O, Le Deist F, Fischer A, Rabourdin-Combe C.

Articles related to Myelin and the Effects of Zinc Deficiency or Mercury Toxicity

Specificity of zinc binding to myelin basic protein.
Neurochem Res 1995 Sep;20(9):1107-13
Riccio P, Giovannelli S, Bobba A, Romito E, Fasano A, Bleve-Zacheo T, Favilla R, Quagliariello E, Cavatorta P.

Effects of low-zinc status and essential fatty acid deficiency on growth and lipid composition of rat brain.
Clin Exp Pharmacol Physiol 1982 Mar-Apr;9(2):213-21
Odutuga AA.

Developmental zinc deficiency and behavior.
J Nutr 1995 Aug;125(8 Suppl):2263S-2271S
Golub MS, Keen CL, Gershwin ME, Hendrickx AG

Biochemical markers of neurotoxicity. A review of mechanistic studies and applications.
Hum Exp Toxicol 1996 Mar;15 Suppl 1:S20-35
Manzo L, Artigas F, Martinez E, Mutti A, Bergamaschi E, Nicotera P, Tonini M, Candura SM, Ray DE, Costa LG.

Magnetic resonance imaging (MRI), neurobehavioral testing, and toxic encephalopathy: two cases.
Environ Res 1993 Apr;61(1):117-23
White RF, Feldman RG, Moss MB, Proctor SP.

Developing brain as a target of toxicity.
Environ Health Perspect 1995 Sep;103 Suppl 6:73-6
Rodier PM.

Articles related to Aluminum and Vaccine Reactions

Adverse reactions after injection of adsorbed diphtheria-pertussis-tetanus (DPT) vaccine are not due only to pertussis organisms or pertussis components in the vaccine.
Vaccine 1991 Oct;9(10):699-702
Gupta RK, Relyveld EH. National Institutes of Health, Bethesda, MD 20892.

Reactions to adsorbed diphtheria-pertussis-tetanus (DPT) vaccine have mostly been attributed to the pertussis organisms or pertussis components in the vaccine. **Nevertheless reactions may also be due to other factors such as sensitization induced by aluminium adjuvants and impurities present in crude toxoids that cannot be removed by purification of toxoids after formalinization.** Aluminium compounds such as aluminium phosphate and aluminium hydroxide are the most commonly used adjuvants with vaccines for human use. **Due to the increasing concern about the toxicity of aluminium, other adjuvants like calcium phosphate may be evaluated as an alternative to aluminium adjuvants.** To minimize reactions after immunization with DPT vaccine due to impurities in the toxoids, the use of toxoided purified toxins is suggested.

(Since this publication no apparent effort has been made by the vaccine manufacturers to correct his issue)

Aluminum compounds as vaccine adjuvants.
Adv Drug Deliv Rev 1998 Jul 6;32(3):155-172
Gupta RK.

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Role of aluminium in skin reactions after diphtheria-tetanus-pertussis-poliomyelitis vaccination: an experimental study in rabbits.
Toxicology 1992;73(1):117-25
Pineau A, Durand C, Guillard O, Bureau B, Stalder JF.

Articles related to Xenobiotic Toxicology

Endocrine modulators: risk characterization and assessment.

Toxicol Pathol 2000 May-Jun;28(3):438-40
Fenner-Crisp PA.
Office of Pesticide Programs, US Environmental Protection Agency, Washington, DC 20460, USA. fenner-crisp.penelope@epa.gov

Over the last several years, information has been accumulating that suggests that adverse effects are being induced in certain wildlife species, and perhaps also in humans, as a consequence of exposure to man-made chemicals that have been released into the environment.

Developmental neurotoxicology of endocrine disruptors and pesticides: identification of information gaps and research needs.

Environ Health Perspect 1998 Jun;106 Suppl 3:807-11
Tilson HA.

National Health and Environmental Effects Research Laboratory, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina 27711, USA.
tilson.hugh@epamail.epa.gov

There is increasing evidence that some environmental chemicals can interrupt neurodevelopmental processes during critical periods of development, resulting in effects on sensory, motor, and cognitive function. It is now generally accepted that developing organisms are differentially sensitive to chemical exposure because of toxicokinetic and/or toxicodynamic factors. Regulatory mechanisms have been implemented to protect humans from over- or inappropriate exposures to environmental chemicals. Current regulatory practices, however, may be insufficient because of the possibility that some environmental chemicals interfere with endocrine function at key periods of neurodevelopment. In addition, a recent National Research Council (NRC) report on pesticide contamination in the diets of infants and children concluded that current regulatory practices may not sufficiently protect infants and children from the risk of pesticide exposure. The NRC report indicates that regulatory agencies might underestimate the actual exposure of infants and children to pesticides and rely too heavily on data from adults in the risk assessment of pesticides. Consideration of endocrine-disrupting chemicals and the differential susceptibility of infants and children has led to identification of a number of information gaps and research needs that should be addressed in order to improve future risk assessments for these chemicals.

Concluding Remarks

I have presented a general overview of the complex biological troubles our children face. It is so complex most physicians have no means for managing it systematically. The typical 10 minute HMO office visit provides no opportunity for the pediatrician or family practitioner to evaluate these conditions. The marked rise in the incidence of autism – currently 1:190 children under age 15 – demands our attention. The subtle effects of environmental toxins, thimerosal, aluminum, vaccines, and antibiotics are likely interacting to disrupt normal neurodevelopment. Continuing efforts at physician education and information systems for parents will be essential. Funding for current medical care needs, as well as research at a clinical level and academic level will also be required. It is suggested that changes in insurance rules mandating coverage for autism related diagnoses are required. Finally, a major overhaul of the vaccine injury compensation rules is necessary.

Respectfully Submitted,

J Bradstreet MD

James Jeffrey Bradstreet, MD, Fellow, AAFP
Director of Research
International Autism Research Center
1663 Georgia Street, #700
Palm Bay, Florida, 32907

Disclosures: Neither I, my wife, IARC, The Good News Doctor, Inc., Creation's Own, Inc., or any other affiliate of mine receives any funding from any government agency for research. Bayer Pharmaceutical has offered but we did not receive a research grant of $130,000 for IVIG research in autism. My son and daughter each own 300 shares of Repligen Corp. stock currently trading at $2.28/share (4/20/2001).

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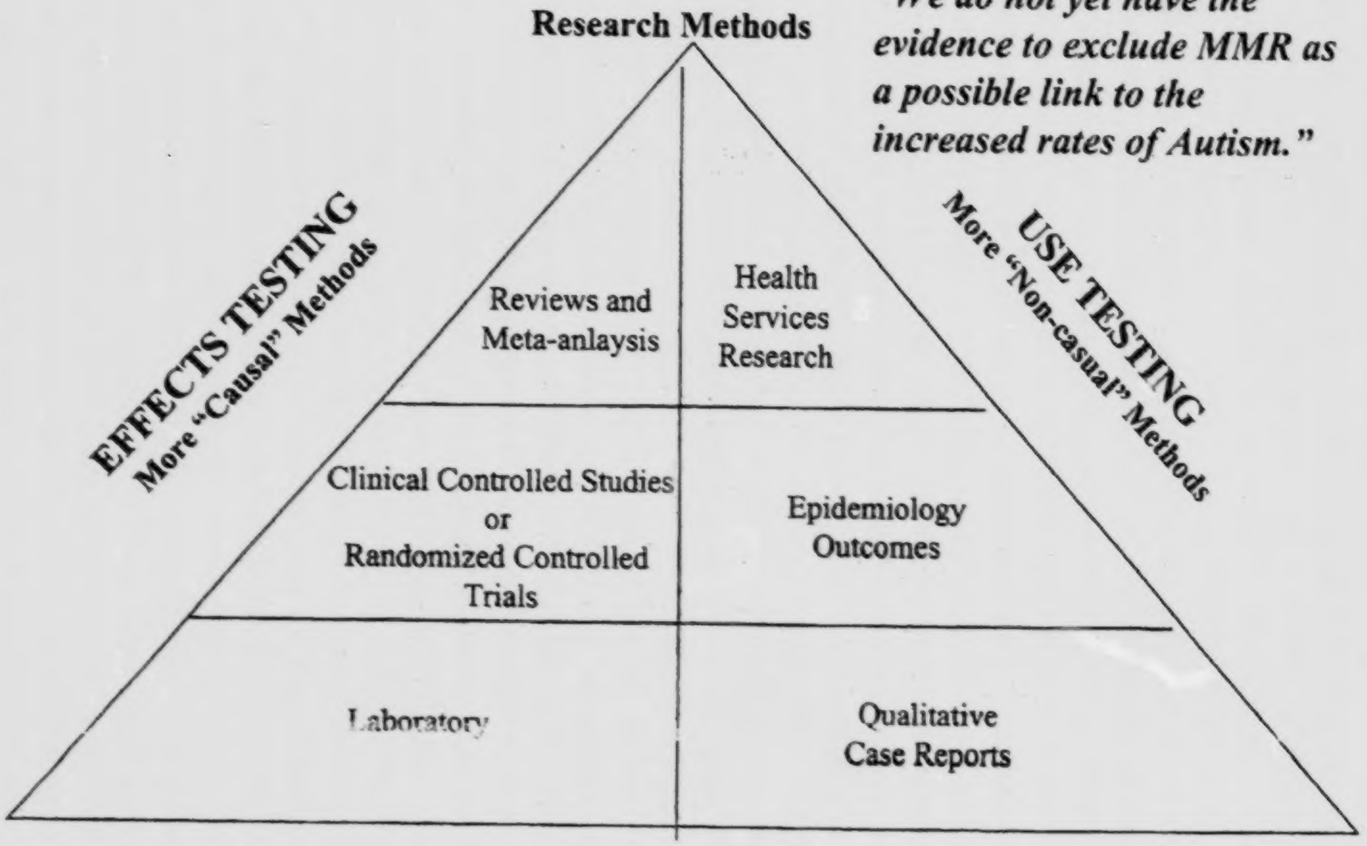
“Balanced” Evidence Hierarchy

“We do not yet have the evidence to exclude MMR as a possible link to the increased rates of Autism.”



Research Methods

EFFECTS TESTING
More “Causal” Methods

USE TESTING
More “Non-casual” Methods

Reviews and Meta-anlaysis

Health Services Research

Clinical Controlled Studies or Randomized Controlled Trials

Epidemiology Outcomes

Laboratory

Qualitative Case Reports

IS MMR LINKED TO AUTISM? EPIDEMIOLOGICAL PERSPECTIVES

Testimony to the Congress of the United States of America

House Committee on Government Reform

April 25, 2001

Walter O Spitzer, M.D., M.P.H., F.R.C.P.C.

Emeritus Professor of Epidemiology, McGill University, Montreal, Canada

15305 Isabella Court, Corpus Christi, Texas, 78418

In a briefing paper for the Institute of Medicine of the National Academy of Sciences of the USA, Soto and colleagues concluded: "… based on the epidemiological evidence to date and the opinion of the authors…, the evidence is inadequate to accept or reject a causal relationship between MMR and autism." **[Reference: Soto MA, Cleary SD, and Foster VB, Commissioned Backround Paper, Institute of Medicine Immunization Safety Review Committee, 2001]** As summarized in this document, submitted to the House Committee on Government Reform of Congress, on April 25, 2001, I reached the same conclusion independently. My views were peer reviewed shortly before the release of the I.O.M.'s briefing document and will be published by Oxford University Press this month. **[Reference: *Adverse Drug Reactions and Toxicological Reviews*, in press]**.

At the turn of this millennium (December '00 and January '01), the public debate about the safety of trivalent measles-mumps-rubella (MMR) vaccine has been intense. A handful of papers with strong views have been published in the medical press. Extensive coverage in the lay press and electronic media has now brought the controversy to the center of the public's attention. I refer to only one example of lay press coverage, a headline in *The Time* of London, "Biggest study clears MMR" [12-XII-2000, p.1].

A cluster of articles in the most recent issue of *Adverse Drug Reactions and Toxicological Reviews* (2000, 19(3) 1-19) has been welcome to those of us who are agnostic about MMR as a possible determinant of autistic syndromes (AuS) with attendant complications. The lead paper of the cluster is a review of the 'state of science' as reflected in part by pre-licensing studies of the safety of MMR vaccine. In it, Wakefield and Montgomery distilled and underscored viewpoints that have characterized their published and ongoing research. To publish anything about MMR/AuS that does not necessarily support "official" mainstream policies or governmental interpretation of evidence is a difficult decision for editors of any journal. I commend the editorial integrity of *Adverse Drug Reactions and Toxicological Reviews* in publishing such controversial articles. It was very wise to publish the evaluations of the four distinguished peer reviewers of the Wakefield-Montgomery article in the same issue. Disquiet among those four British opinion

ANDREA ROSENTHAL

April 30, 2001

Congressman Dan Burton
Via Fax: 202-225-0016

Dear Mr. Burton:

I, like you, strongly believe that the MMR vaccine and vaccines in general are responsible for the autism epidemic. I have read your comments on the IOM MMR report.

I am surprised that the following has not been widely publicized in relation to the report - many believe that the culprit isn't necessarily the MMR alone, but rather the MMR in conjunction with preceding vaccines, most of which contain thimerisol, a mercury based preservative. For those whose bodies cannot remove mercury well, mercury can cause a myriad of injuries, including disrupting the gut. The MMR then attacks the gut and sets off the syndrome documented by Dr. Wakefield. The more vaccines, the more mercury. As the total load of mercury increases, more and more children have trouble removing the mercury and develop symptoms (autism spectrum, learning disabilities, ADHD, communication disorders, etc). While MMR use has increased only slightly in the last decade or so, the TOTAL LOAD of vaccines has increased dramatically – perhaps as dramatically as the increase in autism.

I wrote this information in a letter to the editor of The Washington Post and the letter was printed in the Health section. This is logic the Press can understand. Please consider publicizing this information.

Thank you.

Sincerely,

Andrea Rosenthal

2938 MOTHER WELL COURT • HERNDON, VA • 20171
PHONE: 703-709-7854 • FAX: 703-787-5765

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

APR 25 2001

The Honorable Dan Burton
Chairman
Committee on Government Reform
House of Representatives
Washington, D.C. 20515-6143

Dear Mr. Chairman:

Thank you for your continued interest in childhood vaccines. This letter is in partial response to your letter of April 11, 2001, in which you invited the Food and Drug Administration (FDA or the Agency) to testify at the April 25 hearing on "Autism - Why the Increased Rates? A One year Update." We understand that pursuant to your request, FDA will now testify on the second day of the hearing, April 26, 2001.

FDA takes very seriously the concerns addressed in your letter, and the concerns raised at the hearing held on July 18, 2000, entitled, "Mercury in Vaccines - Are We Taking Unnecessary Risks."

Your request will be restated, followed by our response.

1) **An outline of the actions that the FDA has taken to evaluate the possible link between autism and vaccines to insure the safety of vaccines.**

As described in the July 18, 2000, hearing, FDA continually monitors reports made to the Vaccine Adverse Event Reporting System (VAERS) as part of its post-marketing surveillance program, and this includes review of reports of autism. At the April 26, 2001, hearing, FDA will detail further efforts in this regard.

2) **A list of the research showing the safety of the currently licensed vaccines on the Childhood Immunization Schedule and their ingredients.**

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3) Copies of the research articles and an outline of unpublished research that was submitted as part of these vaccines' approval packages.

The license application for each currently licensed vaccine contains data from the corresponding clinical trials conducted under investigational new drug applications (INDs). We assume that these are the data you refer to as "unpublished research." The data from these clinical trials is the research that FDA evaluates in determining whether a biological product is safe, pure, and potent. Published research articles may be included as part of the IND or a license application or the new drug application (NDA).

In biologics license applications, published and unpublished research is not specifically indexed. Each application contains thousands of pages and finding the requested articles would require a page-by-page review. It would be prohibitively resource intensive for FDA to identify and copy these research articles and to outline all of the unpublished research.

As you know, the Committee has requested the above information in the past, and to accommodate the Committee, we have extended the offer for the Committee to visit the Agency to review the documents contained in the vaccine license files. Ms. Beth Clay, of your staff, has visited the Agency to review the actual documents in the files. We again extend the offer for you or your designee to visit the Agency to review the actual application file documents for the above requested information.

Please note that FDA approved product labeling contains a description of the clinical trials used to demonstrate safety, purity, and potency of vaccines. In July 1999, and again in May 2000, FDA provided the Committee with FDA approved labeling for licensed vaccines, and updated labeling for all product labeling that had been revised. We will provide updated labeling for Aventis Pasteur's DTaP approved in March 2001.

4) Detail the history of thimerosal, the safety data required prior to its inclusion in vaccines, and a list of all licensed vaccines for adults and children with their levels of mercury. Provide to the Committee by April 19th copies of all research submitted to the FDA regarding thimerosal.

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FDA provided answers to these questions in our letter of August 8, 2000, which was in follow-up to the July 18, 2000 hearing. FDA is updating a chart containing the levels of mercury in licensed vaccines and will provide that to you when it is completed.

5) **It is our understanding that the FDA may also be conducting its own research and evaluations regarding thimerosal and mercury. Please provide a complete description of these research activities and their findings.**

FDA's research activities will be described in our testimony.

6) **A chart outlining vaccine adverse events that were reported between January 1, 2000 and April 1, 2001.**

Tab A contains a chart outlining vaccine adverse events that were reported between January 1, 2000 and April 1, 2001.

7) **A report of all licensed vaccines, the number of events per vaccine and provide an analysis regarding the types of events, the seriousness, and the FDA follow-up to the reports.**

Tab B contains several articles describing the VAERS reporting system and analyses of data submitted to VAERS.

FDA previously provided the Committee with a line listing of all VAERS reports from January 1, 2000, until early 2001 (the exact date of each report varies as it took considerable time to prepare the reports). This information was provided to the Committee electronically via seven e-mails sent to Ms. Clay between January 22, 2001 and February 14, 2001.

As agreed to in a telephone conversation on April 18 between Ms. Karen Meister of my staff and Ms. Clay, FDA will provide an update of the previously reported line listings to include reports received through April 1, 2001.

As discussed with Ms. Clay, it is difficult to attribute causality of a particular reported event with a specific vaccine because a particular event may follow vaccination but may also occur in unvaccinated individuals. In addition, adverse events occurring in unvaccinated individuals are not reported, so there is no "control group" to study. Without an unvaccinated group it is usually impossible to assess whether the number of reported events is different from the number that would have been observed in the absence of vaccination. This makes it difficult to determine what fraction, if any, of events following vaccination are related to the vaccine as opposed to other causes. In addition, many vaccines are given in combination, or close in time with other individual vaccines. This contributes to the difficulty in assessing causality, if any, for a particular vaccine and the adverse event.

For this reason, VAERS reports are analyzed in the aggregate to look for patterns that suggest a plausible causal relation between the vaccine and the adverse event. While individual reports are reviewed, causality assessment based on individual reports is usually not possible. Plausible causal associations need to be evaluated in controlled studies.

Please be assured that FDA diligently monitors all VAERS reports as part of our ongoing monitoring of the safety of vaccines.

8) Copies of all reports of autism or encephalopathy resulting in autism or other adverse reactions leading to autism.

TAB C contains a line listing of all VAERS reports from January 1990 through April 2001 for autism. We are not aware of specific adverse reactions that are known to lead to autism.

Please be assured that FDA is committed to ensuring that all licensed vaccines meet the statutory standards of safety, purity, and potency. The introduction and appropriate use of vaccines have prevented countless cases of serious illness and death, and these benefits of vaccination significantly outweigh the theoretical risk posed by the small amounts of thimerosal present in some vaccines.

Thank you again for your continued interest in childhood vaccines. We look forward to the hearing on April 26. In the interim, if you have further questions, please let us know.

Sincerely,

for
Melinda K. Plaisier
Associate Commissioner
for Legislation

Enclosures

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cc: The Honorable Henry A. Waxman
Ranking Minority Member
Committee on Government Reform

Opening Statement
Congressman Bob Barr
Committee on Government Reform
Hearing on "Autism - Why the Increased Rates? A One Year Update"

Mr. Chairman, I thank you for holding this hearing today. You have been on the forefront of this, and many other, healthcare-related issues. I know every parent in America is grateful for your leadership.

Autism is a disease we know too little about. To date, no known factors in the psychological environment of a child have been shown to cause autism. Yet its prevalence rate now places it as the third most common developmental disability; more common than Down's syndrome. Whatever we can do to shed light on the cause, and more importantly, the cure, is needed.

Given that the Measles/Mumps/Rubella vaccine is administered to nearly 4 million children each year, any cause and effect between the vaccine and autism has a potentially huge impact. Therefore, I am encouraged by the preliminary findings of the Immunization Safety Review Committee regarding the hypothesized MMR vaccination correlation to autism.

However, Mr. Chairman, I am sure you are in agreement we should view this report as one of a series, not as the final word on the relationship between MMR vaccinations and autism. This study, though thorough, is inherently limited due to its methodology. Epidemiological studies do not necessarily have the precision to detect occurrences on a population level. In fact, the Immunization Safety Review Committee states as much in its recommendations: "The committee concludes that further research on the possible occurrence of ASD in a small number of children subsequent to MMR vaccination is warranted."

The government has an obligation to ensure that all vaccines are safe, no matter how rare the incidence of adverse reaction may be. Vaccines are the only drugs the government requires us to take. Yet we know that some vaccines contain numerous live viruses, bacterial agents, and other ingredients, such as aluminum, mercury and formaldehyde. We have an obligation to ensure that we are not unknowingly exposing any adult or child to harmful compounds.

Our national immunization program has been, and continues to be, one of the most effective and beneficial tools in public health protection. Yet there continues to exist a high level of concern among parents which must be addressed meaningfully and comprehensively. It is incumbent on us to examine all issues thoroughly. I urge the Institute of Health and the Immunization Safety Review Committee to continue with more precise studies on the correlation between the MMR vaccine and autistic spectrum disorders.

AUTISM—WHY THE INCREASED RATES? A ONE-YEAR UPDATE

THURSDAY, APRIL 26, 2001

HOUSE OF REPRESENTATIVES,
COMMITTEE ON GOVERNMENT REFORM,
Washington, DC.

The committee met, pursuant to notice, at 10:10 a.m., in room 2154, Rayburn House Office Building, Hon. Dan Burton (chairman of the committee) presiding.

Present: Representatives Burton, Gilman, Morella, McHugh, Weldon, Waxman, and Cummings.

Staff present: David A. Kass, deputy counsel and parliamentarian; Mark Corallo, director of communications; S. Elizabeth Clay, professional staff member; Robert A. Briggs, chief clerk; Michael Canty, legislative assistant; John Sare, deputy chief clerk; Corinne Zaccagnini, systems administrator; Kate Anderson, Jon Bouker, and Sarah Despres, minority counsels; Ellen Rayner, minority chief clerk; and Teresa Coufal, minority staff assistant.

Mr. BURTON. Good morning. A quorum being present, the Committee on Government Reform will come to order.

The minority ranking member will be here shortly, as will some of the other panelists. I ask unanimous consent that all Members' and witnesses' opening and written statements be included in the record. Without objection, so ordered.

I ask unanimous consent that all articles, exhibits and extraneous or tabular material be included in the record. And without objection, so ordered.

We're going to be hearing today from the National Institutes of Health, the Centers for Disease Control and Prevention and the Food and Drug Administration. Autism is a neurobiological disorder. It locks a person inside himself or herself. This disorder, which leaves children like my grandson, Christian, unable to express themselves or interact with others, is now at epidemic levels in this country, and I mean epidemic.

One in 400 children in Indiana, 1 in 190 children in Oregon, 1 in 150 children in Brink Township, NJ. How has the Department of Health and Human Services responded to this epidemic? Have our health agencies recognized this dramatic rise and acted accordingly? If we generously estimate that NIH has focused $60 million on autism, and that's generous, autism research out of a $20 billion budget, that would mean that their investment is 0.003, three thousandths of 1 percent.

Does that adequately address an epidemic that affects between 1 in 190 children in Oregon and 1 in 500 children nationwide? I'm including in the record a document taken from the NIH Web site this morning that shows research initiatives at the NIH and their funding for a 3-year period. We'll give you all copies of this, we'd like for you to take that back with you.

According to this document, NIH estimates they will spend $45 million this year on autism. This is compared to $136 million on sleep disorders and $434 million on vaccine development, which could be part of the problem, especially if it's got mercury in it. Two of the issues that were discussed at length yesterday were the concerns that the dramatic rise in autism may be related to the MMR vaccine and mercury exposure through childhood vaccines. We do not yet have enough research evidence to make a conclusion one way or the other. Our health agencies need to fund clinical and laboratory research that will get the answers.

As we learned yesterday, epidemiological studies cannot answer these questions. Epidemiology is important for looking at incidence and prevalence, but not in answering questions about causality. I have a short video showing the effects of mercury on the brain. I think that's simply saying that we're moving to get new vaccines on the market that have little or no mercury. It's a step in the right direction, but I continue to be concerned on behalf of the 8,000 children a day who may be exposed to mercury through their childhood vaccines until the current supply is used up.

And why that isn't being recalled by the health agencies of this country, the FDA, I cannot fathom. As we speak, kids are having mercury shot into their arms, and we know it's a toxic substance. We had toxicology experts here yesterday talking about it and what it does to the brain. We're going to show a video on what it does to the brain.

And yet the people in the health agencies continue to allow that to be done. And I cannot figure out why.

Yesterday we also heard about research that the NIH is funding at the University of Rochester regarding mercury in autistic children. We'll hear today how research is to evaluate the level of mercury in the serum, the hair and the urine of children receiving the currently recommended childhood immunization schedule.

I hope that the reports will include the hair and urine data as Dr. Haley, a leading mercury expert, suggested. Simply reporting the blood data will be misleading. To only report the blood data and not analyze and report the hair and urine samples would be an injustice. We need to look at it all.

And I want to tell you something. We have 113 Members of Congress that have signed up for the Autism Caucus. We're going to end up with about 270, 280. And we're probably going to have over half the U.S. Senate in the caucus. And if you think this is going to go away, you guys are blowing smoke. Because I'm telling you, I'm going to make sure that everybody in the Congress knows the problems and knows what's facing us. If the health agencies don't deal with this and deal with it quickly, you're going to have a big problem over there.

I've also talked to Tommy Thompson, new head of the Health Department. He's going to continue to talk to you, on a regular basis, if we don't do something about this. It's unconscionable that we have thousands and thousands of children being inoculated and vaccinated with vaccines that have toxic substances in them, and we see a horrible increase in the number of people that are autistic and we continue down the same path.

I just don't understand it. Last year the Centers for Disease Control and Prevention reported that they did not know why so many children in Brick Township, NJ, had autism. They conducted a thorough evaluation of environmental toxins and numerous other potential factors, but chose not to include vaccine history as a part of their evaluation and report. Why is this?

I believe vaccines are so important, but why they put three and four and five and six and seven and eight and nine together at one time, with mercury and other toxic chemicals in them into our kids, I just don't understand. We have an epidemic on our hands, and we cannot ignore any potential path that may lead to ending the epidemic.

With that, we have this brief video that we'd like for you to see that shows the effects of mercury on the brain and I hope you'll pay particular attention to this.

[Video shown.]

Mr. BURTON. That test was done in June 1999, almost 2 years ago. I don't know if our health agencies are aware of it, but in your comments today, I hope you'll address whether or not you're familiar with that study, and whether or not our health agencies have done like studies or taken an interest in that and can respond to it.

[The prepared statement of Hon. Dan Burton follows:]

Opening Statement

Chairman Dan Burton
Government Reform Committee

Hearing

Autism – Why the Increased Rates? A One-Year Update. Part II

Thursday, April 26, 2001

2154 Rayburn House Office Building
Washington, DC 20515

Good morning, a Quorum being present, the Committee on Government Reform will come to order.

We will be hearing from the National Institutes of Health, the Centers for Disease Control and Prevention and the Food and Drug Administration today.

Autism is a neurobiological disorder. It locks a person inside himself or herself. This disorder, which leaves children like my grandson, Christian, unable to express themselves or interact with others is now at epidemic levels in this country.
One in 400 children in Indiana. One in 190 in Oregon. One in 150 in Brink Township, New Jersey.

How has the Department of Health and Human Services responded to this epidemic? Have our health agencies recognized this dramatic rise and acted accordingly?

If we generously estimate that NIH has focused sixty million dollars on autism research out of a twenty billion dollar budget, that would mean an investment of .003 % (three thousandths of one percent). Does that adequately address an epidemic that affects between one in 190 in Oregon and one in 500 nation-wide? I am including in the record a document taken from the NIH Website this morning that shows research initiatives at the NIH and their funding for a three-year period.

According to this document, NIH estimates they will spend forty-five million dollars this year on autism. This compared to one hundred thirty six million on sleep disorders and four hundred thirty four million on vaccine development.

Two of the issues that were discussed at length yesterday were the concerns that the dramatic rise in autism may be related to the MMR vaccine and mercury exposure through childhood vaccines.

We do not yet have enough research evidence to make a conclusion one way or the other. Our health agencies need to fund clinical and laboratory research that will get the answers. As we learned yesterday, epidemiological studies cannot answer these questions. Epidemiology is important for looking at incidence and prevalence, but not in answering questions about causality.

I have a short video showing the effects of mercury on the brain. I think that simply saying that we are moving to get new vaccines on the market that have little or no mercury is a step in the right direction, but I continue to be concerned on behalf of the eight thousand children a day who may be exposed to mercury through their childhood vaccines until the current supply is used up.

Yesterday, we also heard about research the NIH is funding at the University of Rochester regarding mercury and autistic children. We will hear today how research is to evaluate the level of mercury in the serum, the hair, and urine of children receiving the currently recommended childhood immunization schedule. I hope that the reports will include the hair and urine data as Dr. Haley, a leading mercury expert, suggested simply reporting the blood data will be misleading. To only report the blood data and not analyze and report the hair and urine samples would be an injustice.

Last year the Centers for Disease Control and Prevention reported that they did not know why so many children in Brick Township, New Jersey had autism. They conducted a thorough evaluation of environmental toxins and numerous other potential factors but chose not to include vaccine history as a part of their evaluation and report. Why is this?

We have an epidemic on our hands and we cannot ignore any potential path that may lead to ending the epidemic.

Mr. BURTON. Do you have an opening statement, Mr. Gilman?

Mr. GILMAN. I want to commend the chairman and our committee for looking into this problem, one that's long overdue, and I thank you for the opportunity to be here.

Mr. BURTON. Thank you, Mr. Gilman. I don't know if you're familiar, but Congressman Chris Smith and Congressman Doyle have formed what's known as the Autism Caucus. I don't know if you're a member yet, but I hope you will join so we can make sure every member is aware of the problems with it.

Let's start with Dr. Rennert. Do you have an opening statement?

STATEMENTS OF OWEN M. RENNERT, M.D., SCIENTIFIC DIRECTOR, NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT, NATIONAL INSTITUTES OF HEALTH; KAREN MIDTHUN, M.D., DIRECTOR, OFFICE OF VACCINE RESEARCH AND REVIEW, FOOD AND DRUG ADMINISTRATION, ACCOMPANIED BY SUSAN ELLENBERG, M.D., DIRECTOR, OFFICE OF VITAL STATISTICS AND EPIDEMIOLOGY; NORMAN BAYLOR, M.D., ASSOCIATE DIRECTOR, REGULATORY POLICY, OFFICE OF VACCINES; AND DR. COLLEEN BOYLE, ACTING ASSOCIATE DIRECTOR, SCIENCE AND PUBLIC HEALTH, CENTER ON BIRTH DEFECTS AND DEVELOPMENTAL DISABILITIES, CENTERS FOR DISEASE CONTROL AND PREVENTION

Dr. RENNERT. Mr. Chairman and members of the committee, I'm Dr. Owen Rennert, Scientific Director of the National Institutes of Child Health and Human Development at the NIH. I appreciate the opportunity to provide information on behalf of the NIH Autism Coordinating Committee about ongoing and planned research activities at the NIH that are relevant to autism and pervasive developmental disorders.

Autism, as you know better than I, is a cruel disorder, not only as a result of the disability it causes, but also because it is an illness that challenges the emotional bond between child and parent. In its most severe forms, it effectively isolates that child socially, cognitively, emotionally and linguistically, denying other family members even the opportunity to console and comfort.

In light of these immense human costs and the significant public health burden that autism brings with it, the NIH is working to focus the research community with ever-greater intensity on this terrible disease. We appreciate the continued involvement that parents have given us in that effort.

The Children's Health Act of 2000 called for expansion, intensification and coordination of autism related scientific programs at NIH. I'm pleased to report that significant progress is being made, including toward the establishment of a new network of centers of excellence in autism. The act directed the Secretary of Health and Human Services to establish an interagency autism coordinating committee, which will include NIH, the Centers for Disease Control and Prevention and other HHS agencies.

Yesterday, Secretary Thompson delegated to NIH authority for establishing this coordinating committee. And we can assure you, it will have at least three members from the parent community of children with autism.

There has been considerable expansion and enhanced coordination of autism research efforts at NIH. The amount of NIH support autism related research grew from $22 million in fiscal year 1997 to $52 million in fiscal year 2000. This demonstrates the commitment of Institute members to the broad intensification of autism research efforts.

As you requested, Mr. Chairman, we have supplied for the record the 10-year funding history of NIH sponsored autism related research, the list of projects funded in fiscal year 2000. We will also be supplying the abstracts of those funded grants shortly.

Effective this week also, NIH has released an RFA, request for applications, containing setaside funds for research support for the development of autism centers applications. This is part of an overall plan to support a variety of investigative teams and wherever possible, to recruit the participation of outstanding investigators who previously have not worked in autism research. These grants would be funded in September 2001 if meritorious applications are submitted.

A second RFA will be issued in fiscal year 2002 to solicit applications for the centers of excellence with funding of the first of these centers targeted for early in fiscal year 2003. NIH anticipates a pool of approximately $8 million per year, which will be available for the first 5 years of the funding of those programs.

The Children's Health Act of 2000 calls upon NIMH, the Institute of Mental Health, to take the lead in providing a program under which samples of tissues and genetic materials are donated, collected, preserved and made available for autism research. NIH presently supports ongoing efforts by Harvard's brain tissue resource center, UCLA and the University of Miami's tissue banks, and recently special supplements were awarded to target acquisition of necessarily biological materials from individual with autism for focused study.

The network. In 1997 through an RFA, the National Institutes of Child Health and Human Development with co-funding from the National Institute of Deafness and Communicative Disorders, established the networks on the neural biology and genetics of autism, referred to as the collaborative programs of excellence in autism.

Currently, we have enrolled nearly 2,300 patients with well diagnosed autism in the network and are gathering data from their families. A major ongoing CPEA initiative, a part of this network that is co-funded by NICHD, NIDCD and the CDC is the autism regression vaccine study. A principal goal of this study is to assess temporal association between measles, mumps, rubella vaccine and the onset of autism and attempts to differentiate early and late onset forms of the disorder.

Another aim of this study is to try to replicate studies of persistent measles infection in children with autism versus those children who are not affected. Stage one of the project, which got underway in September 2000, includes 1,600 well diagnosed cases of autism and 1,250 healthy controls. Individual vaccination records as well as records of the onset of autism, specifically looking at the age of onset, the age of recognition and the age of the diagnosis, will be examined in this study.

Stage two of this project will attempt to replicate previously reported findings regarding abnormal measles antibody titers and persistent measles infection. In this phase, investigators will examine 250 children with early onset autism, 250 children with the regressive form of autism, 250 healthy controls matched to early onset cases, as well as 250 controls matched to regressive autism cases.

Neuroscience research, as you know, requires that we understand the pathogenesis and cause of autism, and is the most promising approach to ultimately developing targeted effective treatments. Until the brain mechanisms responsible for the manifestations of autism are understood, it will not be possible to develop truly targeted interventions.

Treatment research also is currently focused on studying the efficacy and safety of promising treatment interventions which are commonly used in the community without adequate testing or are aimed at specific impairing symptoms. These include both psychosocial and pharmacologic interventions.

Last October, neuroscientists, including autism researchers, parents, advocates and NIH program staff, participated in a 1-day brainstorming session on the role of the environment in autism which was organized by the National Institutes of Environmental Health Sciences. This group identified key priorities, large scale epidemiologic studies to determine autism incidence and prevalence trends, studies to describe the natural history of autism and to identify meaningful subgroups that may be at increased risk from environmental exposures in studies specifically to examine the proposed association between regressive autism and thimerosal in vaccines.

Mr. BURTON. I don't know how much longer your opening statement is, but we'd like to get to the questions as quickly as possible.

Dr. RENNERT. I'll abbreviate it.

I simply would indicate to you that there are ongoing studies of several institutes amongst the ones you mentioned, the one at the University of Rochester, which attempt to look at hair, urine, serum levels of children having received a thimerosal and mercury derivatives, of children having received immunizations, those who have had thimerosal containing vaccines and those who haven't.

Preliminary data, as you were told yesterday, shows no difference in blood levels. I do not have at this point in time the complete analysis, because it hasn't been completed.

There are also studies at several centers that are looking at the pharmacokinetics, the metabolism, the disposition and the disposition in tissues such as brain of mercury when administered as thimerosal, mercurial mercury in monkeys. There are another set of studies that have been funded in November 2000 that are carrying out somewhat similar experiments in rats. These again look at the cellular distribution patterns of mercury in tissue, including the brain, and also are attempting to evaluate the role of immune activation in altering brain levels of mercury after exposure to thimerosal.

The last comment that I'll make in a general way is that as you know, the Children's Health Act authorized a longitudinal study to investigate basic mechanisms of environmental disorders and environmental factors, both risk and protective, that influence health and developmental processes.

In the context of environment, one is talking about chemical, physical, social behavioral influences on children who have critical windows of vulnerability during development, during which time environmental exposures could have a greater influence and diseases of increasing prevalence, such as autism and asthma, are two targeted elements of this. Planning for this study, which will follow about 100,000 children across the United States from birth into adulthood, is currently underway, with pilot studies scheduled to occur in fiscal year 2002.

The other comments I was going to make related exclusively to the efforts of the NIH to increase its dialog with the parents and the public community with regard to what our priorities should be, how we conduct our research as it relates specifically to autism. The only thing to highlight there is as a consequence of those efforts, there is a list server presently available that provides up to date information about autism related research activities at the NIH, there is an NIH Web page which also allows you to identify all the research that presently is funded by NIH and gives you information about advocacy groups, the scientific literature, etc.

In closing, we at NIH understand the passion of parents and families of those who have been affected by autism and related disorders and share your concerns for quickly unraveling the mystery of autism. Thank you, Mr. Chairman.

[The prepared statement of Dr. Rennert follows:]

Statement of Owen Rennert, M.D.
Scientific Director
National Institute of Child Health and Human Development
National Institutes of Health

Committee on Government Reform
U.S. House of Representatives
Washington, D.C.

April 26, 2001

"Autism – Why the Increased Rates? A One Year Update"

Mr. Chairman and Members of the Committee, I am Dr. Owen Rennert, Scientific Director of the National Institute of Child Health and Human Development (NICHD) at the National Institutes of Health (NIH). I appreciate this opportunity to provide information, on the behalf of the NIH Autism Coordinating Committee (NIH/ACC), about ongoing and planned research activities at the NIH that are relevant to autism and pervasive developmental disorders. The NIH/ACC comprises the National Institute of Mental Health (NIMH), NICHD, the National Institute of Neurological Disorders and Stroke (NINDS), the National Institute on Deafness and Other Communication Disorders (NIDCD), and the National Institute of Environmental Health Sciences (NIEHS).

Autism is a cruel disorder, not only as a result of the disability it causes, but also because it is an illness that challenges the emotional bond between child and parent. The family must watch an apparently healthy child slip away, and succumb to a brain disorder that, in its most severe forms, effectively isolates that child -- socially, cognitively, emotionally, and linguistically – denying other family members even the opportunity to console and comfort. It is a disorder that completely changes the rhythms of family life, putting enormous strain not only on parents, but on siblings. And of course, autism does not end in childhood. Often symptoms become even more difficult to manage as the person with autism ages. In light of these immense human costs and the significant public health burden that autism brings with it, the Institutes that comprise the NIH/ACC are working to focus the research community with ever-greater intensity on this terrible disease, and we appreciate continued parent involvement in our efforts.

Last October, Congress passed The Children's Health Act of 2000 (P.L. 106-310). Section 101 of the law called for expansion, intensification, and coordination of autism-related scientific programs at NIH. I am pleased to report the significant progress that we are making, including progress toward the establishment of a new network of Centers of Excellence in Autism Research. This new network of major research centers will bring disciplines including developmental neurobiology, genetics, and psychopharmacology to bear on questions about the causes, early detection and diagnosis of autism, as well as treatment and prevention. The new law calls for greater efforts to collect and share genetic materials and tissue samples, and to provide a means through which the public may both obtain and provide information to the Director of NIH. I will describe our progress toward these ends.

Congress accurately recognized the broad impact of these disorders and directed the Secretary of Health and Human Services to establish an Interagency Autism Coordinating Committee (IACC). The IACC will include NIH, the Centers for Disease Control and Prevention (CDC), and other HHS agencies. Most recently, the Agency for Healthcare Research and Quality and the Agency for Toxic Substances and Disease Registry have requested membership. The law also calls for other Federal departments – for example, the Department of Education – to be represented on the Committee. Dr. Ruth Kirschstein, the Acting Director of NIH, has asked Secretary Thompson to delegate to NIH authority for establishing the IACC. The Act also authorizes the Secretary, at his discretion, to appoint parents or other legal guardians of individuals with autism or other pervasive developmental disorders to the IACC.

Autism Research Initiatives at the NIH

In the few years since the NIH/ACC was established, there has been considerable expansion and enhanced coordination of autism research efforts at NIH. The amount of NIH support of autism related research grew from $22 million in Fiscal Year 1997 to $40 million in FY 1999, nearly doubling in a period of two years. In FY 2000, funding again increased substantially, to approximately $52 million, a sum that encompasses a large number of grants, contracts, and intramural research programs distributed across the NIH. Indeed, this continuing growth demonstrates the commitment of the Institute members of the NIH/ACC to the broad intensification of autism research efforts called for in the Children's Health Act. Most of these ongoing NIH-supported projects are investigator-initiated. Nonetheless, in many cases, NIH actively has taken steps to encourage, structure, and support autism research programs that were ultimately funded. As you requested, Mr. Chairman, I am supplying for the record the 10-year funding history of NIH-sponsored autism related research, and the list of projects funded in FY 2000.

Autism Treatment RFA. Recently, the NIH/ACC has undertaken a new research initiative in the realm of treatment interventions directed at autism symptoms. In November 2000, as a follow-up to a major meeting that they had hosted and supported, the NIH/ACC Institutes issued a Request for Applications (RFA) to solicit research applications on innovative approaches to the treatment of autism. The Institutes have set aside $1,000,000 to fund innovative autism treatment proposals that peer reviewers regard as the most promising. Approximately 30 applications have been received and are scheduled for peer review at the September National Advisory Council meetings.

Reissuance of Autism Program Announcement. In February 2001, the five member Institutes of the NIH/ACC reissued a Program Announcement entitled "Research on Autism and Autism Spectrum Disorders." This announcement clearly states for the research community NIH's continuing interest in and support of research dealing with these disorders.

Centers of Excellence in Autism Research. There are currently no NIH-funded Centers with a primary focus on autism or autism spectrum disorders. The Center grant mechanism, which is currently available to teams of researchers who wish to apply, provides support for multidisciplinary and multi-investigator studies of a specific research problem of a complex nature that requires the application of diverse expertise and methodologies.

As noted above, a major component of the autism provisions of the Children's Health Act of 2000 is the Centers of Excellence in Autism Research program. The NIH/ACC is implementing a strategy for developing these centers. As part of these efforts, the NIH/ACC Institutes intend to release an RFA containing set aside funds for research support for the development of center applications. This is the first stage of an overall plan to support a variety of investigative teams – and whenever possible, to recruit the participation of outstanding investigators who previously have not worked in autism research – in order to maximize the probability that they will become highly qualified applicants for the Centers of Excellence in Autism Research. Each developmental award under this initial RFA will be for one year and a maximum of $100,000 for direct costs. The estimated total funds (direct and indirect costs) available for support for all awards made under the center development grants RFA will be $1.5 million, permitting as many as ten awards, the first of which could be funded in September 2001, if meritorious grant applications are submitted. Let me emphasize that participation in this RFA will not itself be a factor in the review of Center applications. Current grantees, for example, may decide to submit a Center application without participating in this developmental RFA.

A second RFA will be issued in Fiscal Year 2002 to solicit applications for the Centers of Excellence, with funding of the first of these centers early in FY 2003. NIH anticipates that a pool of approximately $8 million per year will be available for the first 5 years, with subsequent investments depending on the sustained quality of applications. Participating NIH Institutes will collaborate in funding the Centers so that they will become an interactive network of high-quality research enterprises covering a spectrum of interests in this disorder.

Brain tissue and genetics resources. The Children's Health Act of 2000 calls upon NIMH to take the lead in providing for a program under which samples of tissues and genetic materials are donated, collected, preserved, and made available for autism research. Post-mortem brain tissue, offers a unique, high-resolution window into the inner workings of brain cells. For example, by using radioactive tracers on sections of brain tissue, scientists can detect and pinpoint any abnormal activity. Only with access to brain tissue can the underlying neuropathology of autism be uncovered. To take advantage of emerging opportunities for discovery in post-mortem tissue made possible by the new molecular methodologies, NIH, in collaboration with the autism advocacy community, has stepped up efforts to expand brain bank collections for the study of autism.

NIH supports ongoing efforts by the Harvard Brain Tissue Resource Center, UCLA's West Los Angeles VA Medical Center, and the University of Miami's tissue bank to collect and make this vital resource available to researchers. Recently, special supplements were awarded to target acquisition of necessary biologic materials from individuals with autism for focused study. The work of the brain banks is coordinated by the Autism Tissue Program through the National Alliance for Autism Research and, of course, through the commitment of families who arrange for tissue donations when individuals with autism die.

Some of the most important clues to the biology of autism will come from genetics. Twin and family studies have shown that genes play a substantial role in autism risk. These studies show that genetic relatedness to a person with autism increases the risk of autism substantially -- indeed far more than is observed in other serious brain diseases such as schizophrenia or manic depressive illness -- and much more than many general medical illnesses, such as type 2 diabetes, that are widely understood to have a component of risk due to genetic susceptibility. However, there is substantial evidence that risk for developing autism does not appear to be due to a single gene in most families, but instead to the interaction of multiple genes. At the clinical level, this explains why autism has a complex pattern of inheritance. For scientists, however, it means that any individual gene may contribute only a small increment of risk, and is thus very difficult to isolate. One of the key needs to solve the genetics of disorders such as autism is a large enough collection of samples. Supported under a contract with Washington University, the NIMH Center for Genetic Studies at Rutgers University has been receiving data and blood samples from NIMH-funded autism genetics projects at Stanford University, New England Medical Center, Vanderbilt University, and the University of North Carolina. These data and biomaterials are widely distributed to the scientific community to conduct analyses on the genetic basis of autism, and their availability is expected to accelerate collaborations among researchers and the discovery of genes producing disease vulnerability.

Network on the Neurobiology and Genetics of Autism: Collaborative Programs of Excellence in Autism (CPEAs). In 1997, in response to the recommendations of the *Autism: State of the Science Conference* held in 1995, and through an RFA, the NICHD, with co-funding from the NIDCD, established the Network on the Neurobiology and Genetics of Autism, referred to as the CPEAs. Each multidisciplinary, often multi-site project is studying some particular basic and clinical aspect of the biological etiology (including possible genetic, immunological, and/or environmental causes), brain structure and function, and clinical course of autism. Each multidisciplinary project has a unique focus and research plan. In addition, all projects use a common diagnostic protocol and common core measures and procedures to collectively address some research questions that are beyond the resources and/or subjects of any single project. Individually or collectively, the CPEAs investigate the causes, diagnosis, early detection, prevention, and treatment of autism. Expertise at the CPEAs ranges from immunology, molecular genetics, and developmental biology, to clinical and developmental pharmacology. The Network also participates in an international autism genetics research consortium that pursues autism research of international import. An RFA to recompete the CPEAs Network will be issued in October 2001, with five years of funding to be awarded.

Coordination of information across CPEAs occurs through regular meetings of the Network Steering Committee. These annual scientific meetings include investigators from all projects and ongoing subcommittee working groups that discuss topics such as genetics, cognitive development, and communication, supplemented with e-mail and telephone conferencing among the directors of the CPEAs. Extensive outreach and sharing of strategies for recruitment and retention make individuals aware of opportunities to participate in the CPEA research projects. Currently, we have enrolled nearly 2,300 people with well-diagnosed cases of autism in the network and are gathering genetic data from their families. Both competitive and administrative funding supplements to these projects have allowed NICHD to take advantage of this shared resource in facilitating the development of methods in genetic analysis, neuroimaging, neuropsychology, and the conduct of clinical research studies.

A major ongoing CPEA initiative that is co-funded by NICHD, NIDCD, and CDC is the Autism Regression/Vaccination Study. A principal goal of the study is to assess temporal association between measles/mumps/rubella (MMR) vaccine and onset of autism, differentiating early- and late-onset forms of the disorder. Another aim of the study is to try to replicate studies of persistent measles infection in autism cases versus healthy controls, which have been widely publicized but remain unproven. Stage 1 of the project, which got underway in September 2000, includes 1,600 well-diagnosed cases of autism and 1,250 healthy controls; individual vaccination records as well as records of onset of autism, specifically looking at age of onset, age of recognition, and age of diagnosis will be examined. Stage 2 of this project will attempt to replicate previously reported findings regarding abnormal measles antibody titers and persistent measles infections. In this phase, investigators will examine 250 early onset autism cases, 250 regressive autism cases (that is, children who develop normally early on, but subsequently regress), 250 healthy controls matched to early onset cases, and 250 healthy controls matched to regressive autism cases.

Treatment Research

Neuroscience research to understand the pathogenesis of autism is the most promising approach to ultimately developing targeted effective treatments. Until the brain mechanisms responsible for the manifestations of autism are understood, it will not be possible to develop truly targeted interventions that can be expected to correct the core features of the disorder.

While neuroscience research on autism continues, treatment research is currently focused on studying the efficacy and safety of promising treatment interventions which are commonly used in the community without adequate testing or are aimed at specific impairing symptoms such as compulsions, stereotyped behavior, overactivity and self-injurious and aggressive behavior. Both psychosocial and pharmacological interventions are being studied.

Medications trials in autism are ongoing in the Research Units on Pediatric Psychopharmacology (RUPP), a research network supported by NIMH contracts and devoted to testing promising pharmacological agents for the treatment of children and adolescents with autism and other pervasive developmental disorders. Two protocols aimed at testing the efficacy and safety of risperidone in the management of youths with autism and suffering from severe agitation, self-injury and other impairing behaviors have recently completed enrollment. The statistical analyses are scheduled to be done this summer, and will be peer reviewed before being released to the public later this year. Another protocol to test the possible therapeutic benefits of

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medications in the management of hyperactivity and impulsive behavior in children with autism and other pervasive developmental disorders is starting at five RUPP sites. Even if these studies cannot be expected to provide treatment that will 'cure' the core features of autism, they will provide useful data that will guide families and clinicians in making treatment choices for individuals with autism who are severely impaired.

Research on Environmental Exposures. Public concern is mounting over the potential relevance of environmental exposures, either before birth or in early postnatal life, to the etiology of autism spectrum disorders. Last October, neuroscientists, including autism researchers, parent advocates, and NIH program staff were invited to participate in a one-day "brainstorming session" on the role of the environment in autism, organized by the NIEHS. The group identified several key research priorities: large-scale epidemiological studies to determine autism incidence and prevalence trends, studies to describe the natural history of autism and to identify meaningful subgroups that may be at increased risk from environmental exposures, and studies to examine the proposed association between regressive autism and thimerosal in vaccines.

The increased interest in the potential linkage between environmental agents and autism coincided with the issuance of a request for applications by the NIEHS to expand their existing network of Centers for Children's Environmental Health and Disease Prevention. The Centers program is funded jointly by the NIEHS and the Environmental Protection Administration. The goal of the latest expansion effort is to increase the number of Centers that study the relation between environmental agents and developmental disorders.

With respect to the broad question of thimerosal-containing vaccines, the National Institute of Allergies and Infectious Diseases (NIAID) currently is supporting several hypothesis-based studies in humans, primates and rodents related to thimerosal and mercury-related compounds. One project being conducted at the University of Rochester Vaccine Treatment and Evaluation Unit (VTEU) and the National Naval Medical Center is designed to: a) determine the level of mercury in the serum, hair and urine of children receiving currently recommended childhood immunizations; and b) compare levels of mercury in children who received vaccines containing thimerosal with those receiving thimerosal-free vaccines. The study was initiated in February 2000. Sixty-three infants were enrolled. Preliminary data show that children who received vaccines with thimerosal did not have more mercury in their blood than children who received vaccines without thimerosal. The investigators are currently conducting final analysis of the data in preparation for publication.

Two studies in rhesus macaques were initiated in November 2000 at the University of Washington. These two studies are designed to: a) determine the pharmacokinetics of thimerosal and methyl mercury in serum and brain tissue in juvenile macaques; and b) examine the metabolism/excretion of methyl and ethyl mercury in infant macaques, as well as deposits in hair/fur during the suckling period.

In collaboration with the NIEHS, NIAID initiated three rodent studies in November 2000. These three studies are designed to: a) compare the distribution of mercury levels in multiple organs after administration of thimerosal, ethyl mercury, and methyl mercury; b) evaluate the cellular patterns of distribution of different forms of organic mercury in the brain after administration of thimerosal, ethyl mercury and methyl mercury; and c) evaluate the role of immune activation in altering brain levels of mercury after exposure to thimerosal.

To address environmental exposures more broadly, the Children's Health Act of 2000 authorized NICHD, along with a consortium of federal agencies including other NIH institutes, the CDC and the EPA, to conduct a major longitudinal study to "investigate basic mechanisms of developmental disorders and environmental factors, both risk and protective, that influence health and developmental processes." In this context, "environment" is defined to include chemical, physical and social-behavioral influences on children, who have critical windows of vulnerability during development, during which time environmental exposures could have a greater influence. A prospective longitudinal study of this magnitude is necessary for answering many questions about childhood diseases and disorders that appear to be increasing, such as autism and asthma. Planning for this study, which will follow about 100,000 children across the U.S. from before birth into adulthood, is currently underway, with pilot studies scheduled for FY 2002-03.

NIH/ACC Annual Scientific Meeting. Each year, the five participating NIH/ACC Institutes organize and convene this conference to focus on a specific, timely topic. The NICHD and NIEHS have taken the lead in developing this year's session on "Potential Cellular and Molecular Mechanisms in Autism and Related Disorders." One theme of particular interest at the meeting, which is scheduled for September 6-7, 2001, will be the development of new animal models and methodologies to study autism and relevant environmental insults to the developing nervous system.

Mechanisms for Public Input. NIH is committed to bringing public views to its activities, programs and decision-making; to conveying information about NIH's processes and progress to a broad public; and to seeking comment about its operations and help evaluating its performance. Each year since 1998 the Directors and scientific program staff of the Institutes comprising the ACC have held a special meeting to invite representatives of autism research advocacy groups to meet with them, and other institute staff, to openly discuss ongoing efforts and future plans with regard to autism. This year, the meeting was held on March 30, 2001. The meeting was well attended, with representatives of all of the major national groups with an interest in NIH activities with respect to autism represented. In addition to the Directors and staff of the NIH/ACC member Institutes, representatives from other NIH Institutes, PHS agencies, and the Department of Education were also present. Frank discussions were conducted regarding many current issues relating to autism research, and over a dozen presentations were made by non-Federal organizations to share their research findings and points of view.

Other current opportunities for public participation include the NIH Director's Council of Public Representatives (COPR) meetings, the individual institute advisory council meetings, and specially conducted public forums around the country. In addition, when appropriate, public reviewers are included to bring their insights and perspectives to Scientific Review Groups for research grant applications.

Public Liaison Offices were formally established within each Institute and Center and in the Office of the NIH Director in 1999. They conduct outreach to constituency groups and serve as a contact point for the public, especially with regard to policy matters. The Office of Public Liaison is also the central point within an institute where members of Congress can refer their constituents. For the last two years, the Information and Public Liaison Officers have held a special meeting with members of the autism advocacy community to exchange information. As a direct result, a listserv has been developed with e-mail addresses of advocacy group members and others who wish to subscribe. AUTISM&LIST.NIH.GOV is a valuable resource for anyone interested in up-to-date information about autism related research activities at NIH. Announcements on the listserv will be automatically archived and the list of available messages also will be available in digest form. The NIH Medline Web site for autism was another significant topic of discussion and increased effort in response to the parent meeting last year (http://medlineplus.nlm.nih.gov/medlineplus/autism.html). This is a searchable site with numerous links related to the latest news, research, scientific literature, autism advocacy organizations, rehabilitation, specific conditions such as Asperger's, related issues such as vaccines, treatment, and the specific NIH/ACC Institutes, which also improved their individual Web sites to provide better information on autism and autism spectrum disorders.

Mr. Chairman, we at NIH have a deep commitment to pursuing the research necessary to defeat autism. We firmly believe that this can be done most effectively by enlisting a larger pool of scientists prepared to do the complex work that is essential for success. That is what we are planning to do with our carefully constructed plan to implement the Children's Health Act of 2000 passed by Congress last year. We at NIH understand the passion of the parents and families of those who have been affected by autism and related disorders, and share your concern for quickly unraveling the mystery of autism. We look forward to working with the scientific community, the Congress, and parents to address this devastating disorder.

I will be pleased to respond to any questions that you and the other members of the Committee may have. Thank you.

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Mr. BURTON. Dr. Midthun.

Dr. MIDTHUN. Mr. Chairman and members of the committee, I'm Dr. Karen Midthun. I'm the Director, Office of Vaccine Research and Review of the Center for Biologics Evaluation and Research, FDA. With me today are Dr. Susan Ellenberg and Dr. Norman Baylor. Dr. Susan Ellenberg is Director of the Office of Vital Statistics and Epidemiology, and Dr. Norman Baylor is the Associate Director for Regulatory Policy in the Office of Vaccines.

Mr. Chairman, as a physician and a parent, I want to express to you, the members of this committee and to parents that I'm aware of the devastating effects of autism on children and their families. I'm here to assure you that we are working diligently to ensure that the vaccines we license for use in the United States are shown to be safe, pure and potent. I appreciate the opportunity to participate in this hearing on autism and to respond to the committee's concerns regarding a potential link between vaccines and autism.

The Office of Vaccines regulates the investigation and licensure of vaccines. FDA's regulatory process for licensing vaccines has for decades served as a model for other countries. To date, the existing data do not demonstrate a causal relationship between vaccines and autism. However, I want to assure this committee, the public and especially parents that FDA takes these concerns seriously.

One concern that has been raised relates to the use of thimerosal, a mercury compound as a preservative in some vaccines. FDA recognizes and supports the goal of reducing exposure to mercury from all sources. Consistent with this goal, for several years, FDA has encouraged manufacturers to develop new vaccines without thimerosal as a preservative, and to remove or reduce the thimerosal content of existing licensed vaccines.

Initial results of this effort were realized at least a year prior to the enactment of the FDA Modernization Act of 1997, with the licensure of new thimerosal-free vaccines. As required by Section 413 of FDAMA, FDA conducted a review of the use of thimerosal in childhood vaccines. A review revealed no evidence of harm caused by thimerosal used as a preservative in vaccines except for local hypersensitivity reactions.

Under the U.S. recommended childhood immunization schedule, the maximum cumulative exposure to mercury from thimerosal at the time of this review in 1999 was within acceptable limits for the methyl mercury exposure set by FDA, the Agency for Toxic Substances and Disease Registry and the World Health Organization. Of note, all these guidelines contain a safety margin and are meant as a starting point for evaluation of mercury exposure, not absolute levels above which toxicity can be expected to occur.

However, during the first 6 months of life, cumulative exposure to mercury in some cases could have exceeded the more conservative limits of the EPA depending on the specific vaccine formulations used and weight of the infant. The clinical significance of exceeding EPA's limits is not currently known. Nevertheless, reducing exposure to mercury from vaccines is warranted and achievable, in part because in the United States, it is possible to replace multi-dose vials with single dose vials, which do not require a preservative.

I am pleased to be able to report substantial progress in the efforts to reduce thimerosal exposure from vaccines. At this time, all routinely recommended licensed pediatric vaccines being manufactured for the U.S. market contain no thimerosal or contain only trace amounts in the final formulation. Prior to the recent initiatives to reduce or eliminate thimerosal from childhood vaccines, the maximum cumulative exposure to mercury by routine childhood immunizations during the first 6 months of life was 187 and a half micrograms. With the newly formulated vaccines, the maximum cumulative exposure during the first 6 months of life will now be less than 3 micrograms of mercury, more than a 98 percent reduction.

In an effort to better characterize any toxicity that could have accompanied an exposure to thimerosal from vaccines, FDA is in the process of nominating thimerosal to the National Toxicology Program for further study.

Reports of developmental delay following vaccination have been submitted to the Vaccine Adverse Event Reporting System [VAERS]. Although VAERS reports by themselves usually cannot establish a causal relationship between a vaccine and an adverse outcome occurring after vaccination, further study of these reports can sometimes provide important clues and suggest directions for further research.

FDA takes these reports seriously and has begun a followup study of VAERS reports of autism. In addition, FDA is pursuing research involving the characterization and development of an animal model for autism. While looking at ways to improve the safety of vaccines, we must keep in mind that childhood vaccines have contributed to a great reduction in vaccine preventable diseases, including polio, measles and whooping cough.

Today, it is rare for American children to experience the devastating effects of vaccine preventable illness. However, vaccines, like all medical products, are not risk free, and FDA is committed to continuing its efforts to reduce these risks whenever possible.

In conclusion, FDA continues to work diligently with manufacturers to eliminate or reduce exposure to mercury from thimerosal in vaccines. As stated previously, at this time, all routinely recommended licensed pediatric vaccines being manufactured for the U.S. market contain no thimerosal or contain only trace amounts in the final formulation.

Although no causal relationship between vaccines and autism has been established, FDA, along with other Health and Human Service agencies, continues to pursue research activities to increase our understanding of any potential relationship between vaccines and neurodevelopmental disorders. Although the prevention of disease through the use of vaccines is a tremendous public health accomplishment, there is more work to be done. I assure you that the Office of Vaccines at FDA will continue to make regulatory decisions or recommendations regarding vaccines based on the best scientific evidence to protect the public health.

Mr. Chairman, I appreciate the committee's interest in this area, and look forward to continuing to work with you on this in the future.

[The prepared statement of Dr. Midthun follows:]

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Food and Drug Administration
Rockville MD 20857

STATEMENT BY

KAREN MIDTHUN, M.D., DIRECTOR

OFFICE OF VACCINES RESEARCH AND REVIEW

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

FOOD AND DRUG ADMINISTRATION

DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE

COMMITTEE ON GOVERNMENT REFORM

UNITED STATES HOUSE OF REPRESENTATIVES

APRIL 26, 2001

RELEASE ONLY UPON DELIVERY

INTRODUCTION

Mr. Chairman and Members of the Committee, I am Karen Midthun, M.D., Director, Office of Vaccines Research and Review (OVRR), Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration (FDA or the Agency). OVRR regulates the development and licensure of vaccines. We appreciate the opportunity to participate in this hearing on autism and to respond to the Committee's concerns regarding a potential link. between vaccines and autism. It is important to note that to date, the existing data do not demonstrate a causal relationship between vaccines and autism. Nevertheless, we want to assure this Committee, the public, and, especially the parents that are here today, that FDA takes these concerns very seriously and we want to explain FDA's ongoing efforts in response to the issue of vaccines and autism.

Childhood vaccines have contributed to a significant reduction of vaccine-preventable diseases, (e.g., polio, measles, and whooping cough). In fact, vaccine preventable infectious diseases are at an all-time low and now it is rare for American children to experience the devastating effects of these illnesses. Before vaccines were routinely administered, there were over 175,000 cases of diphtheria annually (1920-22), over 147,000 cases of pertussis (1922-25), and over 503,000 cases of measles (1951-54) reported in the United States (U.S.). These diseases have essentially disappeared in countries with high vaccination coverage, such as the U.S. Up until 1985 and the introduction of an infant vaccine, an estimated 20,000 cases of invasive Haemophilus type b disease, primarily meningitis, occurred annually in the U.S. Now, because of vaccination, the number of cases of invasive Haemophilus b disease has been decreased by more than 98 percent. All of the diseases mentioned above were associated with significant mortality and morbidity.

Background

Like all products regulated by FDA, vaccines undergo a rigorous review of laboratory and clinical data by highly trained scientists and clinicians to help ensure the safety, purity, and potency of these products. From an FDA regulatory perspective, there are four stages in vaccine development: the pre-investigational new drug (IND) stage (before the product is used in people), the IND stage (where human use occurs under limited study conditions), the license application stage for vaccines (where FDA reviews the results of the clinical studies and the manufacturing process), and the post-licensure stage (following approval of the product for marketing).

A sponsor seeks licensure of a complete product as it is formulated for use, not of individual components. Evidence of any acute toxicity from the use of an investigational drug, including vaccines, is included in safety data from human clinical studies, as required under Title 21, Code of Federal Regulations (CFR) Part 312. If any ingredient or ingredients causes acute toxicity, the pre-market safety data would most likely indicate acute toxicity from use of the vaccine product. Such data, however, generally would not show whether any particular ingredient or combination of ingredients is the source of toxicity.

Like other approved drug and licensed biological products, vaccines licensed for marketing may also be required to undergo additional, Phase IV, studies to further evaluate the vaccine or to address specific questions about the vaccine. For example, the manufacturer of Varicella Virus Vaccine committed to perform a post-licensure study with fifteen years of safety follow-up. These studies will provide information about the effects of the

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vaccine in a population larger than that exposed during clinical trials. If additional side effects are identified during the post-marketing phase, either pursuant to adverse event reports filed by health care providers or consumers, or pursuant to Phase IV studies, FDA would take appropriate regulatory action to protect the public health such as, among other options, changing the product's labeling information to reflect the possible side effects, or, in cases of imminent or substantial hazard to the public health, ordering a recall of the product.

Because of the complex manufacturing processes for most biological products, each product undergoes thorough laboratory testing for purity, potency, identity, and sterility. Manufacturers may release lots only after this testing is documented. FDA may require lot samples and protocols showing results of applicable tests to be submitted for review, and where appropriate, further testing by FDA. The lot release program is part of our multi-part strategy that helps ensure product safety by providing a quality control check on product specifications.

Vaccine Adverse Event Reporting System

Licensure of all vaccines marketed in the U.S. is based on a benefit-to-risk analysis of the safety and efficacy data submitted by sponsors to FDA. During the pre-market review process, manufacturers and FDA focus on identifying and understanding risks before an overall risk-benefit decision can be made on the product's licensure. When using any drug or medical product, a patient runs the risk of experiencing reactions. For pharmaceuticals, including vaccines, these reactions are commonly termed "side effects." They usually are identified in clinical trials conducted before licensure and are described in a product's labeling. Known side effects, discovered in the course of clinical trials, upon which a product's licensure or approval is based, comprise the majority of reported adverse events after licensure.

Like all other medical products, vaccines are not entirely risk-free. While serious complications are rare, they can occur. Vaccines are unique medical products in that they are generally administered to a large number of healthy individuals, primarily children. Therefore, it is very important to identify even rare adverse reactions. CBER and the Centers for Disease Control and

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Prevention (CDC) jointly manage the Vaccine Adverse Event Reporting System (VAERS), a cooperative program for vaccine safety. VAERS is a post-marketing safety surveillance program that collects information about adverse events that occur after the administration of U.S. licensed vaccines. An "event" is simply an outcome. However, any outcome that an individual, whether a health care provider or a consumer, believes may have resulted from the administration of a vaccine may be reported to VAERS. Such report will be included in the system, regardless of whether there appears to be a causal relation to the vaccine. Under FDA regulations, 21 CFR, Subpart D - Reporting Adverse Experiences, section 600.80, licensed vaccine manufacturers must report to FDA adverse experience information, and establish and maintain records.

It should be emphasized that adverse event reports can be made by anyone, including health care professionals, patients, and parents. If a patient's physician does not file a VAERS report, the patient can do so. FDA protects the confidentiality of patients for whom an adverse event has been reported. FDA encourages individuals to report to VAERS any clinically significant adverse event occurring after the administration of any vaccine licensed in the U.S. Individuals who want to make a report to VAERS can call VAERS at a toll-free number, 1-800-822-7967, to obtain a reporting form. Forms and reporting instructions also are available on the Internet at www.fda.gov/cber/vaers.html and at www.vaers.org.

Follow-up Study of VAERS Autism Reports

FDA has taken seriously VAERS reports of developmental delay following vaccination and wants to assure the public that the Agency is researching any possible relationship between vaccines and autism. CBER proposes to conduct a follow-up study of VAERS reports of autism. As part of the study, CBER, in conjunction with outside autism experts, will review available medical records and develop an interview questionnaire for parents and others who have reported autism after vaccinations. The goal of the interviews is to gather information about demographics, clinical features, potential risk factors, family history, vaccines administered, time interval from vaccination to autism onset, rapidity of symptom onset, and interval from diagnosis to submission of reports. Though this study cannot determine whether vaccines cause autism, it might suggest hypotheses that could be further evaluated in subsequent controlled, epidemiologic studies.

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Autism-related Laboratory Activities

FDA is actively pursuing research involving the characterization and development of the first virus-induced animal model for autism - Borna disease virus (BDV) infection of the neonatal rat. There is no direct evidence for any relationship between BDV infection and human autism. However, BDV is used as the environmental damaging agent because it infects the brain of newborn rats. It is important to note that BDV is not a cause of autism. The damage it does and the disease syndrome it produces in rats are used only as a "model" to study general biological principles of autism. The features of this model, which FDA scientists have developed over the past ten years, have excellent correlation with what is known about human autism including neuroanatomical, behavioral, and neurochemical correlations. This model is being used in laboratories throughout the U.S. and internationally.

Thimerosal

FDA, together with other U.S. public health agencies, recognizes and supports the goal of reducing exposure to mercury from all sources. Consistent with this goal, FDA has encouraged manufacturers for several years to develop new vaccines without thimerosal as a preservative and to remove or reduce the thimerosal content of existing, licensed vaccines. This joint effort by manufacturers and FDA is reflected by the licensure of thimerosal-free products such as Comvax [Haemophilus b Conjugate Vaccine and Hepatitis B Vaccine (Recombinant) manufactured by Merck & Company, Inc.], licensed October 2, 1996, Infanrix [Diphtheria and Tetanus Toxoids and Acellular Pertussis (DTaP) manufactured by GlaxoSmithKline], licensed January 29, 1997, and Prevnar (Pneumococcal 7-valent Conjugate Vaccine manufactured by Wyeth-Lederle Vaccines and Pediatrics), licensed on February 17, 2000, and the removal or reduction of thimerosal from previously licensed products.

In response to section 413 of the Food and Drug Administration Modernization Act (FDAMA) of 1997, FDA conducted a review of the use of thimerosal in childhood vaccines. Our review revealed no evidence of harm caused by thimerosal used as a preservative in vaccines, except for local hypersensitivity reactions. Under the U.S. recommended childhood immunization schedule, the maximum cumulative exposure to mercury from thimerosal, at the time of this review in 1999, was within acceptable limits for the methyl mercury exposure set by FDA, the Agency for Toxic Substances and Disease Registry, and the World Health

Organization. Of note, such guidelines contain safety margins and are meant as starting points for evaluation of mercury exposure, not absolute levels above which toxicity can be expected to occur. However, the maximum cumulative exposure level exceeded the more conservative limits of the Environmental Protection Agency (EPA). The clinical significance of exceeding EPA's limits is not currently known.

Nevertheless, reducing exposure to mercury from vaccines is warranted. This is achievable, in part, because it is possible in the U.S. to replace multi-dose vials with single dose vials, which do not require a preservative.

We are pleased to be able to report substantial progress in the effort to reduce thimerosal exposure from vaccines. At this time, all routinely recommended licensed pediatric vaccines that are currently being manufactured for the U.S. market, contain no thimerosal or contain only trace amounts of thimerosal. The vaccines with trace amount of thimerosal licensed to date contain less than 0.5 micrograms of mercury per dose, that is, a given dose of vaccine contains less than 1 part per million.

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Our efforts over approximately the past year and a half to accomplish this goal include the licensure of a thimerosal free Hepatitis B Vaccine (Recombinant) manufactured by Merck and Company in August 1999. FDA licensed another hepatitis B vaccine with trace amounts of thimerosal, manufactured by GlaxoSmithKline in March 2000. A supplement for a new formulation of Aventis Pasteur's DTaP Vaccine with only a trace amount of thimerosal was approved in March 2001. Additionally, Wyeth-Lederle Vaccines and Pediatrics now only markets a single-dose, thimerosal-free formulation of its Haemophilus b Conjugate Vaccine in the U.S.

Therefore, all routinely recommended U.S. licensed pediatric vaccines are now available in either thimerosal-free formulations or in formulations that contain only trace amounts of thimerosal. The routinely recommended vaccines include hepatitis B Vaccine, Haemophilus b Conjugate Vaccine, Measles Mumps and Rubella Vaccine, Pneumococcal Conjugate Vaccine, DTaP Vaccine, Inactivated Polio Vaccine, and Varicella Vaccine. Prior to the recent initiative to reduce or eliminate thimerosal from childhood vaccines, the maximum cumulative exposure to mercury via routine childhood vaccinations during the first six months of life was 187.5 micrograms. With the newly formulated vaccines, the maximum cumulative exposure during the first six months of life will now be less than three micrograms of mercury; this represents a greater than 98 percent reduction in the amount of mercury a child would receive from vaccines in the first six months of life.

Thimerosal and the National Toxicology Program

The National Toxicology Program (NTP) was established in 1978 by the Secretary of the Department of Health and Human Services (DHHS or the Department) to coordinate toxicology research and testing activities within the Department; to provide information about potentially toxic chemicals to regulatory and research agencies and the public, and to strengthen the science base in toxicology. The NTP has become a world leader in designing, conducting, and interpreting animal assays for toxicity and/or carcinogenicity.

NTP uses a chemical nomination and selection process as a means to best use its resources with respect to the testing of chemicals of greatest health concern. Member agencies of the NTP, including FDA, are the primary sources of nominations to the NTP. Because of the continued interest on the part of the

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public, as well as public health agencies, to better characterize the potential toxicity that could have accompanied an exposure to thimerosal from vaccines, FDA is in the process of nominating thimerosal to the NTP for further study to adequately assess gaps in knowledge regarding, among other things, neurodevelopmental toxicity.

CONCLUSION

Vaccines provide a great public health benefit in reducing or eliminating vaccine preventable diseases. Like all medical products, there are risks with vaccines and FDA is committed to continuing its efforts to ensure the safety of vaccines. We have worked diligently with manufacturers to eliminate or reduce exposure to mercury from thimerosal in vaccines. As stated previously, all licensed vaccines currently being manufactured for the U.S. market that are on the routine childhood immunization schedule have formulations that are thimerosal-free or contain only trace amounts of thimerosal. Although no causal relationship between vaccines and autism has been established, FDA, along with other DHHS agencies, continues to pursue research activities to increase our understanding of any relationship between vaccines and neurodevelopmental disorders.

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We thank you for your leadership in this area. I would be happy to answer any questions you might have.

Mr. BURTON. Thank you.

Dr. Boyle.

Dr. BOYLE. Good morning, Mr. Chairman and members of the committee. I'm Dr. Colleen Boyle, Acting Associate Director for Science and Public Health in the newly established Center on Birth Defects and Developmental Disabilities at the Centers for Disease Control and Prevention.

I have with me today Dr. Roger Bernier, an epidemiologist and Associate Director of Science for the National Immunization Program at the CDC.

Thank you for the opportunity to update you on CDC's activities related to autism. One major change since last year is that CDC has established, at the direction of Congress, a new center, the National Center for Birth Defects and Developmental Disabilities. This center will increase CDC's efforts to discover causes and develop preventive strategies for birth defects and developmental disabilities, including autism.

First, Mr. Chairman, I want to stress that CDC is committed to understanding the prevalence of autism, identifying its preventable causes and establishing and evaluating prevention programs. We've made considerable progress over the last year toward fulfilling this commitment. Last year, we mentioned that CDC and the Agency for Toxic Substances and Disease Registry were about to report on an investigation on the prevalence of autism in Brick Township, NJ. The investigation found a rate in Brick that is high compared to many previous studies.

However, there are few very recent studies, none in the United States, that have reported rates in this range, which suggest that the rate of autism may be considerably higher than previously thought. To increase our ability to monitor autism prevalence in the United States, in September 2000, CDC competitively funded health departments in Arizona, South Carolina, Maryland and New Jersey to establish monitoring programs for autism in their States.

CDC is also completing the analysis of the first year of autism monitoring data gathered from its own metropolitan Atlanta developmental disability surveillance program. Our report should be complete later this year.

This September, as directed by Congress, CDC will competitively fund up to four centers of excellence in autism epidemiology to conduct collaborative epidemiologic studies. The research objectives of these studies will be determined by an independent oversight committee, and representatives from parent and consumer groups will be invited to provide input to the oversight committee in planning the epidemiologic study.

CDC has also developed a wide range of activities that are responsive to the needs of parents of children with autism and health care professionals working with these children. For example, CDC funds a program at Marshall University in West Virginia of an intensive community support program for families with young children with autism. As part of the centers for excellence in autism and epidemiology, we expect to fund projects of model intervention programs for children with autism, of the economic and social costs of autism, and of studies to look at the natural history of autism.

Some parents have expressed concern about the potential link between autism and vaccines. Although the weight of the scientific evidence does not support such a link, CDC is committed strongly to assuring vaccine safety. The concerns raised regarding autism and vaccines have focused primarily on thimerosal, a preservative in some vaccines, and on the measles, mumps and rubella vaccine. Today, all manufacturers are producing for immunization only vaccines that are free of thimerosal or have only trace elements of thimerosal.

As shown in figure one of my testimony, the thimerosal content of pediatric vaccines purchased by States through CDC's contract has dramatically decreased since 1998. CDC is actively investigating whether there have been any adverse effects related to thimerosal in vaccines. Preliminary analyses of the vaccine safety data link have not supported a link between thimerosal containing vaccines and autism.

It has been suggested that vaccination, particularly with the MMR vaccine, may be related to the development of autism. Substantial scientific review does not support this suggestion. First, the American Academy of Pediatrics executive committee stated in March 2001 that there is a considerable body of evidence that does not support a causal relationship between MMR vaccine and autism or inflammatory bowel disease. Second, the IOM stated just this week that existing evidence does not favor a causal relationship between the MMR vaccine and autism.

In addition, Dales et al. recently reviewed changes over time in the MMR coverage and autism diagnoses in California. There was a 373 percent relative increase, in the prevalence rate of autism between 1980 and 1994 while the MMR immunization coverage was relatively flat over that same period.

To date, the weight of the scientific evidence does not support a causal relationship between vaccines and autism. Nevertheless, because of the continuing concern of parents, we are committed to conducting research to evaluate this matter. At present, we are conducting a study in Atlanta, another in Denmark, and we are collaborating with NIH, with their centers and programs of excellence in autism to further examine the relationship between vaccines and autism.

While we must remain vigilant to assure the safety of vaccines, we must also remember that vaccines benefit the individual child and the public by protecting persons from the consequences of infectious diseases. While we've made great progress to reduce the number of cases of vaccine preventable diseases, threats posed by vaccine preventable diseases are known and are real.

We want to assure you that CDC knows how important it is to find the causes of autism and prevent this disorders. We are committed to conducting research that will lead to these answers. With the support of Congress, we have made a good beginning by funding autism monitoring programs with several States and the Centers of Excellence in Autism Epidemiology to look at causes of autism. CDC's efforts will continue until we have found the answers that will enable us to prevent this serious condition that affects so many American children.

Thank you, Mr. Chairman and members of the committee, for the opportunity to testify before you today. Dr. Bernier and I would be happy to answer any questions that you may have.

[The prepared statement of Dr. Boyle follows:]

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

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TESTIMONY OF

COLEEN BOYLE, PH.D.

ACTING ASSOCIATE DIRECTOR FOR SCIENCE AND PUBLIC HEALTH
NATIONAL CENTER ON BIRTH DEFECTS AND DEVELOPMENTAL DISABILITIES
CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC)

BEFORE THE

COMMITTEE ON GOVERNMENT REFORM
U.S. HOUSE OF REPRESENTATIVES
APRIL 26, 2001

Good morning Mr. Chairman, Congressman Waxman, and members of the Committee.

I am Dr. Coleen Boyle, Acting Associate Director for Science and Public Health in the newly created National Center on Birth Defects and Developmental Disabilities at the Centers for Disease Control and Prevention (CDC). I have with me today Dr. Roger Bernier, an epidemiologist and Associate Director for Science of the National Immunization Program at CDC.

Thank you for the opportunity to testify today about autism and update you on the autism-related activities the agency has undertaken during the year since your last hearing. One major change since last year is that CDC now has established, at the direction of Congress, a new center – the National Center on Birth Defects and Developmental Disabilities. This new center, which I represent today, will increase CDC's efforts to discover causes and develop prevention and intervention strategies for birth defects and developmental disabilities. Over the next few years, CDC hopes to expand monitoring, research, and prevention activities on key birth defects and developmental disabilities and to promote the health and wellness of people with disabilities. Monitoring the prevalence of autism and conducting epidemiologic research on the causes and risk factors of autism will be among the major activities of this new center.

My field of expertise is monitoring and looking for causes of developmental disabilities, a diverse group of physical, cognitive, psychologic, sensory, and speech impairments

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that are usually identified between birth and age 18. Autism is one of the more serious of these developmental disabilities. It is a life-long disability characterized by impairments in social interaction and communication and a pattern of restrictive, repetitive and stereotypic behaviors, interests, and activities. The impact of autism on children and their families is tremendous. Most children with autism require long-term care and services, including special education and supervised care.

CDC's role in preventing developmental disabilities, including autism, is to determine the scope of the problem, identify preventable causes, and establish and evaluate prevention or intervention programs. There is much that is not known about autism. We do not have good data on the scope of the problem – data on the incidence rate in the United States are almost non-existent. Some studies in the1960s and 1970s found rates of 4 to 5 per 10,000 children. Studies since 1985 outside the United States reported about 12 per 10,000 children. A few recent studies, including one conducted by my program which I will mention later, found much higher rates. We do not know if these higher rates are due to different diagnostic criteria, better recognition and reporting, study phenomena, or if they represent a true increase in rates of autism.

The causes of autism remain unknown for most children. Genetics clearly plays a role in autism. Certain exposures during pregnancy are associated with autism, such as alcohol, some prescription drugs such as thalidomide, and infections such as rubella. Clearly more epidemiologic research is needed to find the causes of autism.

CDC'S EFFORTS TO MONITOR RATES OF AUTISM

During the last year, CDC has engaged in a number of activities that have enhanced our understanding of the current prevalence of autism. In late April of 2000, CDC in collaboration with the Agency for Toxic Substances and Disease Registry (ATSDR) released a report of a prevalence study of autism in Brick Township, New Jersey, where local citizens were concerned that the number of children with autism in the community seemed unusually high. CDC was asked to assist in this study by the New Jersey Department of Health and Senior Services because of the complexity of trying to determine the prevalence of autism and the fact that CDC was developing the scientific methods for monitoring this disorder. The investigation found 60 children with an autism spectrum disorder (a category that includes autism and other related disorders) with 36 of these children meeting the criteria for autistic disorder, from a population of about 9,000 children. This corresponds to rates of 6.7 per 1,000 children for autism spectrum disorder and 4.0 per 1,000 children for autism. While the rate in Brick is high compared to many previous studies, there are a few very recent studies – but none in the U.S. – that have reported rates in the range reported in Brick Township.

To address the uncertainty of the finding in Brick Township as well as the lack of autism prevalence data for the U.S. in general, CDC funded in 2000, through a competitive process, state programs in Arizona, South Carolina, Maryland/Delaware, and New Jersey to establish monitoring programs for autism. In this first year of the grant awards, CDC is working with these states to establish a common case definition and methods to identify children with autism, so that data are accurate and can be used for national projections.

In addition, CDC is completing the analysis of the first year of autism monitoring data from the CDC Metropolitan Atlanta Developmental Disabilities Surveillance Program. This program has been monitoring other serious developmental disabilities in the Metropolitan Atlanta area since 1991. Autism was added to the program in 1998 because of concern expressed by parents, educators, and clinicians about possible increases in the prevalence of this condition. A report on the prevalence of autism in 3- to 10-year-old children in greater Atlanta should be completed later this year and will be made available to the public.

Accurate prevalence data are important to understand how many children are being affected and whether that number is increasing, decreasing or constant. But those data can do even more. The database provided by a good monitoring program can be used to conduct studies of causes and risk factors for autism. In FY 2001, Congress directed CDC to establish Centers of Excellence in Autism Epidemiology. These Centers will monitor the prevalence of autism; conduct a collaborative epidemiologic case-control study to identify the causes and preventable risk factors for autism; and develop special Center projects. This year CDC will fund, through a competitive process, four such Centers. Establishing these Centers will increase the number of states that monitor the prevalence of autism and, importantly, will begin the process of collecting data for a large collaborative epidemiologic study to address possible causes of autism, including the role of environmental and genetic factors in the development of autism. The specific research objectives of the epidemiologic studies will be determined by an independent oversight committee. Representatives from autism parent advocacy groups will have an opportunity to provide input to the oversight committee during the planning phase of the epidemiologic study. CDC has successfully used this model to study the causes of birth defects and we believe that it will work equally well for autism and other developmental disabilities.

HOW HAS CDC RESPONDED TO THE NEEDS OF PARENTS AND PROFESSIONALS REGARDING QUESTIONS ON THE CAUSES AND TREATMENT OF AUTISM?

CDC has a wide range of activities to respond to questions from parents and health care professionals.

Since 1995, CDC has funded a program at Marshall University in West Virginia which provides an intensive training program and develops community support for families with young children with autism. The project addresses the needs of the family as a unit as well as the challenging behaviors of the child with autism. The program's goals are to reduce familial stress levels, to increase family access to community resources, to provide parents and educators with a positive-behavior support training program, to facilitate family support teams that help families apply knowledge gained from the training program, and to disseminate the family focus model to other states.

Another way that CDC tries to address the needs of parents is to encourage the Centers of Excellence in Autism Epidemiology to provide information to parents as one of the activities of the Center. Each center will establish a center-specific study from a list of suggested topics provided in the program announcement. Some of those topics are the development, implementation, and evaluation of intervention programs for children with autistic spectrum disorder and their families; the evaluation of economic costs; and the natural history of autism, including associated developmental disabilities and secondary conditions.

CDC has established a way for parents and others to be able to ask CDC scientists questions or express concerns about autism. We have a telephone number (770-488-7400) and a website (cdc.gov/ncbddd/dd/ddautism.htm) with information on how to contact us regarding the causes and treatments for autism and other developmental disabilities. A CDC scientist/clinician provides information about CDC-related activities on autism, addresses questions related to the causes or treatments of autism, and identifies scientists or clinicians in the community who may provide more detailed information. As the autism state monitoring programs and the Centers collect sufficient data on the prevalence and possible causes and risk factors for autism, these data will be made available in aggregate form to parents, researchers and other interested parties by a clearinghouse or network developed jointly by CDC and our state and academic partners. These data will be made available on our website as well as be published in print.

CDC'S COMMITMENT TO VACCINE SAFETY

Some parents have expressed concerns about a potential link between autism and vaccines currently being used in the United States. Although the weight of scientific evidence does not support such a link, CDC is strongly committed to assuring vaccine safety. CDC is actively involved in detecting and investigating vaccine safety concerns and supporting a wide range of vaccine safety research to address safety questions. A critical part of our vaccine safety effort is the objective, scientific evaluation of safety concerns by independent experts. In collaboration with NIH and other U. S. Public Health Service agencies, CDC requested the Institute of Medicine (IOM) to conduct independent reviews by independent scientific experts to determine: 1) whether the available scientific information favors, or does not favor, vaccines playing a role in causation, 2) the level of public health priority the concern should receive, and 3) recommendations for research. As you know, the IOM issued a report this week on the possible role of MMR vaccine relative to autism. The IOM committee concluded that the evidence favors rejection of a causal relationship at the population level between MMR and autistic spectrum disorders. At its next meeting, in July 2001, the IOM will next be evaluating the role, if any, of thimerosal in developmental disorders, including autism, with a final report expected within 60-90 days of that meeting.

A second effort is to create a vaccine safety infrastructure to evaluate safety concerns. As a cornerstone of that effort, in 1990 CDC established the Vaccine Safety Datalink (VSD), a large linked database that includes all vaccinations given through the participating health plans. The VSD project allows for scientific estimation of rates of adverse events in the absence of vaccination to be compared with the rates following vaccination. This is one of the best epidemiologic tools to evaluate whether vaccines play a causal role in adverse events. CDC has expanded the VSD to enhance CDC's ability to investigate safety concerns. Three new sites have been added since last year, for a total of seven managed cared organizations that participate in the network, covering more than 2 percent of the birth cohort of the entire United States. Funding for the independent management of the VSD is awarded through a competitive process. The American Association of Health Plans currently manages the project.

CONCERNS ABOUT AUTISM AND VACCINES

The concerns raised regarding autism and vaccines have focused primarily on thimerosal, a preservative in some vaccines, and the measles, mumps, rubella (MMR) vaccine.

Thimerosal

Despite the fact that thimerosal preservative has been effective in lowering the risk that vaccines could be contaminated by bacteria leading to serious infection, the United States Public Health Service agencies, including NIH, FDA, HRSA, and CDC, working collaboratively with the American Academy of Pediatrics and the American Academy of Family Physicians, took action in mid-1999 to begin removing thimerosal preservative from the vaccine supply. While the risk of harm from this source was only theoretical, the decision was made as a precautionary measure. The elimination of thimerosal preservative from vaccines was judged a feasible means of reducing an infant's total exposure to mercury in a world where other environmental sources of exposure may be more difficult or impossible to eliminate.

As a result of this action, all manufacturers of routinely recommended licensed pediatric vaccines are now producing for the U.S. market only vaccines that are thimerosal-free or contain trace amounts of thimerosal. The vaccines are supplied in single-dose vials which eliminates the need for a preservative.

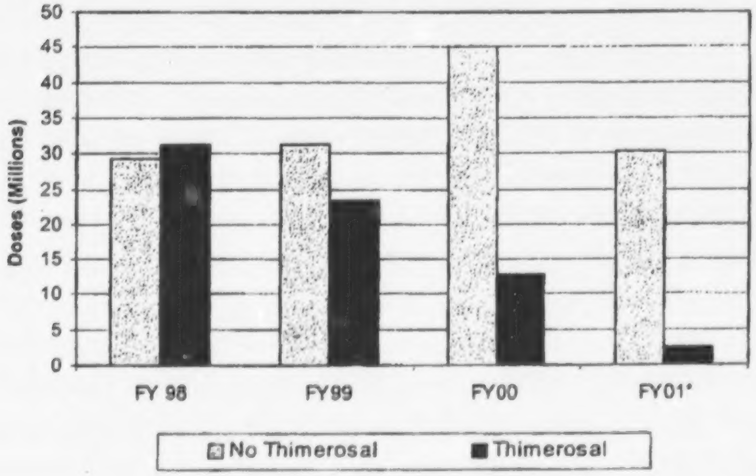
- The two hepatitis B vaccine manufacturers received licenses for vaccines that are either thimerosal-free or contain trace amounts of thimerosal in August 1999 and March 2000, respectively. Since June 2000, CDC has purchased only thimerosal free hepatitis B vaccine or hepatitis B vaccine with only trace amounts of thimerosal for infant immunization.

- Since June 2000, CDC has purchased only thimerosal free *Haemophilus influenzae* type b (Hib) vaccines or Hib vaccine with only trace amounts of thimerosal. Historically, only 1 of 3 Hib manufacturers produced Hib vaccine with thimerosal as a preservative.

- As of March 31, 2001, all of the Diphtheria/Tetanus/acellular Pertussis (DTaP) vaccine produced is free of thimerosal or has only trace amounts of thimerosal.

Figure 1 illustrates that the purchase of pediatric vaccines by States which contain thimerosal as a preservative, through the CDC contracts, has dramatically decreased since 1998.

Figure 1. Pediatric Vaccines Purchased Through CDC Contracts by Thimerosal Content and Fiscal Year, 1998 through 2nd Quarter 2001



*FYO1 data only covers through the 2nd Quarter of FY01
Note: "No Thimerosal" category includes vaccines with no thimerosal or only trace amounts

CDC has not only supported a policy to remove thimerosal preservative from the childhood vaccine supply, it is also, along with other PHS agencies, actively investigating whether there have been any adverse effects associated with thimerosal-containing vaccines. The VSD is being used to examine the risk of neurologic disorders, including autism, associated with the use of vaccines that contain thimerosal as a preservative. In the preliminary screening phase of this investigation, no association was observed between exposure to thimerosal-containing vaccines and 12 of the 17 renal and neurologic conditions studied. A weak statistical association was observed for the other five conditions--language delays, speech delays, attention deficit hyperactivity disorder (ADHD), unspecified developmental delays, and tics. To determine whether the correlation could be seen and confirmed in an independent data base, an effort was made to collect similar data from another managed care organization. Preliminary data from that organization showed no association for speech delays, language delays or ADHD.

To further review this matter, CDC recently convened a panel of independent consultants to obtain their individual input to assist in development of a study to examine whether thimerosal-containing vaccines result in neurodevelopmental disorders in children. The consultants included experts in the fields of toxicology, neurodevelopmental psychology, speech and language, autism, pediatrics, statistics, and epidemiology, as well as a consumer representative. They provided guidance on the best research design, to address issues ranging from study site selection to which battery of standardized neuropsychological tests to administer. In addition, the consultants commented on the need for further studies on specific clinical syndromes, such as autism. CDC is presently analyzing the written comments and revising the research protocols.

MMR Vaccine

It has been suggested that vaccination, particularly with the MMR vaccine, may be related to the development of autism. At least two major hypotheses have been raised:

(1) whether MMR vaccine triggers autism shortly after vaccination, and (2) whether the increase in autism diagnoses in California and elsewhere is due to the increasing use of MMR vaccine.

The suggestion that MMR vaccine triggers autism is based on some reports of cases of autism in which parents noted the onset of autistic behaviors shortly after MMR vaccination. However, scientific studies presented at last year's autism hearing and newer information argue against MMR playing a causal role. If MMR vaccine contributed to the development of autism, one would expect to see clustering of cases after MMR vaccination when a representative sample of cases with autism is evaluated. However, as discussed last year with this Committee, no such clustering was found in a review of more than 400 cases of autism by Dr. Brent Taylor, Head of the Department of Pediatrics and Child Health on the Royal Free Campus of the University College, London. The study's findings were published in the medical journal *The Lancet* in June 1999.

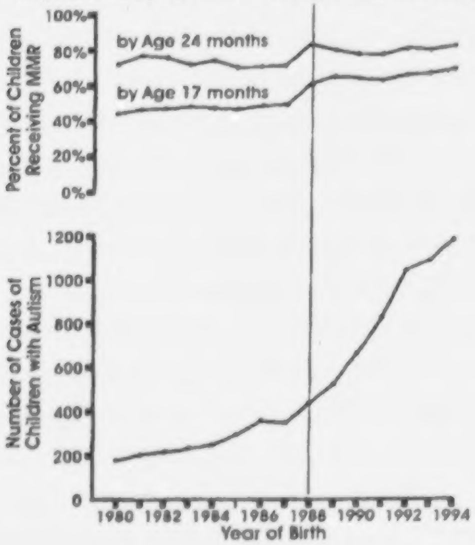
The American Academy of Pediatrics (AAP), an organization of more than 55,000 pediatricians and pediatric specialists, hosted a multi-disciplinary, international workshop on June 12-13, 2000 to review the evidence regarding a possible association between MMR vaccine, inflammatory bowel disease and autism spectrum disorders, especially autism with regression. A detailed Technical Report based on presentations at the workshop and an exhaustive review of the scientific literature will be published in *Pediatrics* in May 2001.

The AAP Executive Committee, in the AAP News in March 2001, stated that there is a considerable body of evidence that does not support a causal relationship between MMR vaccine and autism or inflammatory bowel disease. No data exist to suggest that separate administration of measles, mumps and rubella vaccines would offer any potential benefit over the MMR vaccine currently used in the United States. Furthermore, the Executive Committee expressed concern that such an approach would result in many underimmunized children. Therefore, the Academy continues to support fully the 2001 Immunization Schedule, which also is endorsed by CDC and the American Academy of Family Physicians.

Another of the suggestions for a possible association between MMR vaccination and autism is that the prevalence of autism diagnoses has been increasing in California, and other areas, due to increasing use of MMR vaccine. While there has been an increase in cases being diagnosed, there is scientific dispute whether this increase reflects the incidence of more autism, or better diagnosis and detection. Regardless, substantial scientific evidence does not support a role of MMR vaccine in the reported increases.

Dales, et al, recently reviewed changes over time in MMR coverage and autism diagnoses in the California Department of Developmental Services regional service center system, as published in the *Journal of the American Medical Association*. As shown in Figure 2, there was a 373 percent relative increase in autism case numbers between 1980 and 1994, while the MMR immunization coverage was relatively flat over the same period, increasing only 14 percent. Thus, the data were clear that MMR could not have been responsible for the increase in autism diagnoses seen in recent years.

Figure 2. Percentage of Children Receiving Measles-Mumps-Rubella (MMR) Immunization in Second Year of Life and Caseload of Children with Autism, by Year of Birth, California, 1980-1994



Source: JAMA, 2001, Vol 285, No. 9, p1184

A similar epidemiological study in the U.K., by Kaye, et al, in the *British Medical Journal*, also did not find an association between MMR vaccination and autism. The study used a large database of medical practices in the UK and compared diagnoses of autism over time with MMR vaccination. MMR vaccination was constant at 95 percent

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from 1988 to 1999. However, they found a sevenfold increase in the incidence rate of newly diagnosed cases of autism in this same time period.

CONTINUING CDC RESEARCH

The weight of scientific evidence does not support a causal relationship between vaccines and autism. Nevertheless, because of the continuing concerns of parents, CDC is committed to conducting research to evaluate this matter. Such research includes:

- A study in the metropolitan Atlanta area to evaluate any association between MMR vaccination history and autism. More than 700 children aged 3-10 years old with autism were identified from CDC's Metropolitan Atlanta Developmental Disabilities Surveillance Program from the first completed year of autism monitoring by that program. The vaccination histories of these children will be compared with more than 2100 control children. A final report from this study will undergo peer review in the latter part of 2001.

- A case-control study will be conducted in Denmark to investigate the relationship between the timing of receipt of the MMR vaccine and the risk for autism. Denmark has long-established national disease and administrative registries that can be linked via a unique personal identification number. This allows linking databases of health care, social, and educational services. Children with autism will be identified in the Danish Psychiatric Central Registry and in other databases of children with autism and other developmental problems. A comparison group will be randomly selected from the Danish Central Person Registry. Cases and controls will be linked, via their Danish personal identification number, with their vaccination records in the Public Health Insurance Registry. Also, newborn blood samples from each child can also be obtained from the Danish Biobank of Newborn Bloodspots (established in 1982 for blood samples retained after routine testing of all newborns for metabolic disorders) to test for possible biomarkers for autism apparent before onset of autistic symptoms and vaccination. Finally, supplemental risk factor data for the analyses will be obtained from the Medical Birth Register (perinatal data) and the Prevention Register (sociodemographic data). This is a 3-year study and will be completed in 2004.

- CDC, NIH, and ten NIH-funded Centers and Programs of Excellence in autism are collaborating on a case-control study of developmental regression. Each of the ten Centers was awarded funds through the NIH competitive process. This study is planned to evaluate associations between MMR vaccination and onset of autistic regression; the study will also evaluate measles antibody levels and measles nucleic acid sequences in white blood cells of both cases and well controls.

- CDC is collaborating with FDA on a study that follows up Vaccine Adverse Event Reporting System (VAERS) reports of autism along with a review of medical records of the cases. The VAERS contract also was awarded through a competitive process. Questionnaires will be submitted to individuals who submit reports (usually parents) of possible autism cases, and medical records will be reviewed, when available, to obtain information to classify the cases using standard diagnostic criteria to determine whether they meet the criteria for autism and, if so, the type of autism spectrum disorder.

BENEFITS OF VACCINES

While we must remain vigilant to assure the safety of vaccines, we must also remember that vaccines benefit the public by protecting persons from the consequences of infectious diseases. Vaccines are often cited as one of the greatest achievements of biomedical science and public health in the 20th century. We can point to the remarkable success we have had in controlling numerous infectious diseases that used to be widely prevalent in the United States, including polio, measles, and pertussis (whooping cough). In fact, several of these vaccine-preventable infectious diseases are known to cause developmental disabilities; these diseases include *Haemophilus influenzae* type b (Hib) and congenital rubella syndrome (CRS), one of the few known causes of autism. Rubella vaccine, by preventing CRS, is an anti-autism vaccine. Prior to routine immunization with Hib vaccine, of young children who developed Hib meningitis, 5 percent died and another 15 to 30 percent were left with residual brain damage leading to language disorders and mental retardation.

While we have made great progress in reducing the number of cases of vaccine-preventable diseases, the threats posed by vaccine-preventable diseases are known and real. The viruses and bacteria that cause vaccine-preventable diseases still circulate in the U.S. and around the world. A measles epidemic in the United States led to more than 55,000 cases of measles and more than 11,000 hospitalizations in the three years from 1989 to 1991. Additionally, pertussis has continued to be a public health threat. For example, in 1999, there were 7297 cases of pertussis in the United States, with 15 reported deaths. Continued high U.S. vaccination rates are crucial to prevent the spread of these diseases among U.S. children.

CONCLUSION

We want to assure you that CDC knows how important it is to find the causes of autism and prevent these disorders. We are committed to conducting the research that will lead to these answers. With the support of Congress, we have made a good beginning by funding autism monitoring programs in several states and the Centers of Excellence in Autism Epidemiology to look for causes of autism. We will continue to conduct research on vaccine safety. CDC efforts will continue until we have found the answers that will enable us to prevent this serious condition that affects so many American children.

Thank you, Mr. Chairman and members of the Committee, for the opportunity to testify before you today. I would be happy to answer any questions that you may have.

Mr. BURTON. I neglected to have you sworn. Would you all please stand?

[Witnesses sworn.]

Mr. BURTON. Dr. Boyle, why is it that there's a reduction in thimerosal in vaccines that are being produced today? Did not our health agencies request that thimerosal be removed from vaccines as the newly produced vaccines?

Dr. BOYLE. I think we've made considerable progress in reducing the thimerosal content.

Mr. BURTON. So you've asked that thimerosal be reduced in vaccines, have you not?

Mr. BERNIER. I think the answer is that this was done as a precautionary measure.

Mr. BURTON. Why?

Mr. BERNIER. Because it was feasible to do, and there are sources of exposure to mercury that we cannot control, such as that from food. So——

Mr. BURTON. I'm talking about the vaccine. Why is it that you have started at our health agencies to reduce the amount of thimerosal in vaccines, as a precautionary measure?

Mr. BERNIER. As a precautionary measure.

Mr. BURTON. OK, as a precautionary measure. That would lead one to believe that you're not really sure whether or not thimerosal causes some problems. Otherwise, why wouldn't you just leave it in there and say, hey, we've run all these tests, there's no causal link whatsoever? So why even move to take it out of there?

Mr. BERNIER. There is a theoretical risk.

Mr. BURTON. OK, so there's a theoretical risk. Then why have we not recalled the vaccines that have thimerosal in them right now, while you're testing this? If there's any question whatsoever about what we're putting into our kids' arms, and their bodies, and if you're reducing thimerosal because you think there may be a causal link, as a precautionary measure, why don't you recall the thimerosal that's in doctors' offices that are being injected into kids as we speak until you're sure? Because obviously you're not sure or you wouldn't be taking it out anyway. Why don't you recall it?

Mr. BERNIER. I can give you my comments. The FDA may wish to weigh in on this issue of recall. But as succinctly as I can put it, Mr. Chairman, being safe means being safe from disease as well as being safe from the side effects of vaccine.

Mr. BURTON. Let me ask you this question, then. Can you create a measles vaccine and do we have a measles vaccine that does not have thimerosal in it?

Mr. BERNIER. Yes, that's correct.

Mr. BURTON. Can we create a mumps vaccine that does not have thimerosal in it?

Mr. BERNIER. That's correct.

Mr. BURTON. Then why are you putting thimerosal in it?

Mr. BERNIER. At the present time, as Dr. Midthun and Dr. Boyle mentioned, we have made very good progress, and I can say to you we are not putting in thimerosal any longer in the vaccines that are being produced.

Mr. BURTON. So if you're not, if you're not, as a precautionary measure, then why are you leaving vaccines on doctors' shelves and in drugstores around this country that are being used in facilities where they supply them, are being used, if you're not putting them in new vaccines, as a precautionary measure? Why don't you recall the supply that you have out there until you are absolutely sure, beyond any doubt, that thimerosal has no causal link to autism? Why don't you recall it?

Dr. Midthun.

Dr. MIDTHUN. Under the Public Health Service Act, in order to make a mandatory recall of vaccine, there has to be an imminent or substantial hazard to the public health. As the weight of the evidence does not support a causal link between thimerosal——

Mr. BURTON. Then why are you taking it out of the new ones?

Dr. MIDTHUN. As Dr. Bernier said, it's a precautionary measure. It's recognized that mercury in large doses is toxic and any way that we have of reducing the exposure to mercury over which we have control is something that is desirable to do.

Mr. BURTON. Let me tell you, my grandson was very healthy and very normal and spoke and ran around like every other child. He got nine vaccines in 1 day. He got 41 times what's the allowable amount of mercury through thimerosal in 1 day. And 10 days later, we lost him. Now, we're trying to get him back.

Now, there's a lot of parents out there that are getting all these shots when their children's immune systems are depressed, they've got colds, and they're getting these shots, several of them at a time, with thimerosal in them. As a precautionary measure, if you think there may be a causal link, don't you have any latitude whatsoever to recall those and say, we're not going to destroy this, but we're going to hold these supplies in abeyance until we know for sure, until all the tests have been done?

Dr. MIDTHUN. Not under the Public Health Service Act. That's not what would allow us to make a mandatory recall.

Mr. BURTON. But you are taking thimerosal out of vaccines, as a precautionary measure?

Dr. MIDTHUN. That's correct.

Mr. BURTON. How long are these studies going to take, Dr. Rennert?

Dr. RENNERT. We hope to have answers of various phases within the next 2 to 3 years.

Mr. BURTON. Oh. Do you know how many kids are going to be vaccinated today? Do you know that in California, it used to be one child every 6 hours was becoming autistic. It's now one every 3 hours. In the United States, 1 out of 400 to 500 kids are autistic. And in some parts of the country, it's under 200. And boys have a four times more prevalence of getting autism than girls.

So if you go to Oregon, 1 out of 190 kids are autistic, that means 1 out of 50 boys being born are going to be autistic. And you're telling me these studies are going to take 2 to 3 years, and at the same time the studies are going to take 2 to 3 years, you're going to keep mercury in vaccines that you just saw from that Calgary, Canada study what mercury does to brain cells?

I mean, come on. If there's any doubt whatsoever, and you say it's a precautionary measure you're taking, then why in the heck don't you get that stuff off the market until you've tested it thoroughly? And if it's going to take 3 years, put it some place for 3 years, in a storage box, and if the tests don't prove out, you've still got it, and the pharmaceutical companies can still get their money.

Now, on these tests that you're doing, you said you're testing the blood for mercury. Are you testing hair and urine samples?

Dr. RENNERT. Yes. In the studies that were done by Navy and the University of Rochester, there are samples that have been obtained for study of hair and urine concentrations as well.

Mr. BURTON. Have you had any results from that yet?

Dr. RENNERT. No, sir. The study as far as I know has just been completed and the analysis is occurring. I don't have the data.

Mr. BURTON. How long will it take to get that analysis?

Dr. RENNERT. I would imagine—to be honest, sir, I don't know. I don't think it will be long, but I will attempt to find out and give you an answer.

Mr. BURTON. We would like to have copies of the analysis as quickly as you get them. We'd like to have any records that you have whatsoever about the analyzing of blood, hair, urine, whatever it is, regarding mercury and thimerosal in these kids.

You know, you were talking about how vaccines have reduced measles, mumps, rubella, diphtheria, all these other things. And that is great. And we really appreciate what vaccines and pharmaceutical companies have done for this country. Because they've saved a lot of lives. And what you've done has been very laudable.

But when you have a child who is autistic, from the time he becomes autistic until he dies, they estimate that the cost to our society is $5 million, for each child. Now, if we have 1 in 400, and the cases are rising at a very rapid rate, do you have any idea what that's going to do to our economy? Not now, but 5, 10, 15, 20 years from now. And so every precaution that should be taken must be taken and must be taken now. Because this is not only a health issue, it's an economic issue that's not going to go away.

I mean, we're talking about trillions and trillions of dollars if we don't find an answer. If you've got substances, aluminum, formaldehyde, mercury, in these vaccines, and you have this huge rise and you're not absolutely sure that mercury's not causing it, you ought to get it out of there. You ought to recall this stuff. Because the doctor just said, Dr. Bernier just said that they are producing and can produce vaccines without mercury in them, without thimerosal.

Now, granted, you might not be able to put three or four different vaccines in one vial. Because as I understand it, you put the mercury in there to keep everything pure so they can be used, and won't be tainted. But if you go to single vials with single vaccines, sure, the parents would have to have more shots. But if it's going to be safer, then why not do it? And why wait 3 years for studies if you think that there may, even the most remote possibility, be a causal link.

If you look at some of these studies, like we've seen, and I am not a scientist, I'm not a doctor, I'm just a grandfather who has an autistic kid, and I didn't even know what autism was until a couple of years ago. But when you see the huge number of people that are contacting us through e-mail and through conferences, there's one going on right here, you've got to take the proper precautions. You can't say, let's wait 3 years and let this go on.

So as I said earlier, and I'm going to yield to my colleagues here, as I said earlier, we have 113 members in the Autism Caucus. They will be supplied with every bit of information we get, not only from you folks, but from Calgary, Canada, and from around the world and from the experts we have here. And I will be taking special orders on the floor of the House. I'll be going down there on a regular basis, reading into the record and talking to the American people, about the problems that we have.

So the pressure that you're feeling, if any, now, I don't know if you are or not, but the pressure you're feeling right now is going to be magnified as many times as I can make it, until our health agencies either come to some conclusion that's scientifically provable, or they get that stuff out of there, in particular thimerosal. And I don't know why, if you're coming up with vaccines that don't have these toxic substances in them, as I believe they are, I don't understand why you don't recall that stuff. Get it off the market.

FDA, can you do a voluntary recall for manufacturers the same as the rotavirus recall?

Dr. MIDTHUN. That was not a voluntary recall. The manufacturer on their own initiative withdrew their product from the market.

Mr. BURTON. Can you contact the people that manufacture thimerosal, and I know who it is, can you ask them to recall it temporarily?

Dr. MIDTHUN. That would be something that would be voluntary on their basis.

Mr. BURTON. You can't write them a letter and say that because of the concern of thousands and thousands of parents and because we're in the process of doing research on this, we think it would be prudent to recall thimerosal products until we run all of our tests, which may take as much as 3 years?

Dr. MIDTHUN. I'm sure that the companies are well aware also of these concerns over autism——

Mr. BURTON. But you can't even write them a letter?

Dr. MIDTHUN. It's their choice to make a voluntary recall, and they know that they have that choice, sir.

Mr. BURTON. So you're not going to do anything?

Dr. MIDTHUN. Under the PHS Act, we can make a mandatory recall for the reasons that I indicated. And the company, of course, on its own volition, can do anything it would like in terms of making product available or deciding not to distribute it any longer.

Mr. BURTON. I found out yesterday that there's a lawsuits pending, I believe in, I think it's Mississippi, regarding mercury toxicity and how it's affected children. And if that lawsuit is successful by the people who are bringing the suit, it will probably involve a great deal of money to the pharmaceutical company that produces this product, and other pharmaceutical companies that use it in their vaccines.

I wonder, I just wonder if perhaps one of the reasons why FDA is not pounding these pharmaceutical companies to get this off of the market, especially when you look at this Calgary study about mercury and the toxicity of it, maybe there's not pressure being exerted by pharmaceutical companies on our health agencies because they're afraid of what might happen in that lawsuit if they do withdraw it from the market. Is there any validity to that kind of thinking?

Dr. MIDTHUN. I really couldn't say. I do not know, sir.

Mr. BURTON. OK, Mr. Gilman.

Mr. GILMAN. Thank you, Mr. Chairman. I want to thank you for raising these issues.

Permit me to request that my opening statement be made part of the record.

Mr. BURTON. Without objection.

[The prepared statement of Hon. Benjamin A. Gilman follows:]

OPENING STATEMENT,
BY CONGRESSMAN BENJAMIN A. GILMAN
4/26/2001

①

Opening Statement for Government Reform Hearing on Autism April 25, 2001

I would like to welcome the panel ~~and~~ of EXPERTS BEFORE US AND I thank Chairman Burton and my fellow committee members for investigating why the autism rate has increased AND WHAT WE CAN DO TO ENCOURAGE RESEARCH ON AUTISM. Autism impacts society in a myriad of ways and this hearing will ASSIST US IN addressING several issues that arose during the investigation. It is important ~~to~~ understand how ~~we~~ TO define autism, why the autism rate is increasing, and how we can support effective research that will benefit those who are affected by autism.

Autism is a disease that affects an individual's ability to communicate and interact with people and their environment. While autism may not have been a common disease during my childhood, the Center for Disease Control and Prevention estimated that autism rates have increased from affecting 1 in 10, 000 children to 1 in 500 children. If autism is not

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(2)

affected by race, ethnicity, socio-economic, and educational factors, then what does affect ~~the~~ THIS increasing rate of autism? Due to a lack of information this question may be harder to answer than perceived.

This Committee's investigation has determined that there is a lack of support for biomedical research into the causes, prevention, and effective treatments of autism. This research is essential to our ability to help those who are affected by this disease.

IT IS GRATIFYING ~~I am glad to see~~ that my colleagues Christopher Smith and Mike Doyle are co-chairing the Congressional Caucus on Autism. This caucus will prove to be successful in building support for essential research.

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Hopefully,

At this hearing scientific perspectives will be combined with personal perspectives ~~in hopes of gaining~~ INORDER TO PROVIDE a better understanding of how autism can be aided.

A disease that paralyzes communication, we ~~cannot~~ SHOULD NOT paralyze our own communication between the medical community, the government sector, and those affected by autism.

I look forward to hearing from our panelists and working with all of you as we research the causes and effects of autism.

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Mr. GILMAN. And I do have several questions. I think what Chairman Burton is raising I think is quite pertinent. I'm surprised to hear that, Dr. Midthun, you're reluctant to issue any letter to the manufacturers if there is some concern. You say there is some mandate in the legislation that permits you to make some of these corrections?

Dr. MIDTHUN. Under the PHS Act, the FDA can make a mandatory recall if there is an imminent or substantial hazard to the public health. And as I noted before, the preponderance of the evidence does not suggest that there was a causal relationship between thimerosal containing vaccines and autism. Thus, there is no substantial or imminent hazard that would authorize us to make a mandatory recall, sir.

Mr. GILMAN. And yet, you are making a request that the thimerosal not be included in the future production of vaccines because of some concern? Is that correct?

Dr. MIDTHUN. As Dr. Bernier noted, wherever it is possible to reduce exposure to mercury, that is a goal that we would like to achieve. Because there are many aspects of exposure that we don't have control over. For example, environmental food intake and thus, it's considered a precautionary measure that we can take. It's achievable, we can move from multi-dose vials that require a preservative to single dose vials. That's what we have been doing, and actually have made a substantial achievement toward reaching, as I noted before, currently all vaccines being manufactured for pediatric use under the routine childhood immunization schedule, either contain no thimerosal or only trace amounts.

Mr. GILMAN. And that's based on your recommendations?

Dr. MIDTHUN. That's based on working collaboratively together with the other public health service agencies and also the manufacturers, that it was agreed that this would be an achievable goal, and it would be good to reduce the exposure to mercury whenever possible.

Mr. GILMAN. So there is a consensus in the thinking of the medical world that it would be preferable to eliminate that possibility in providing vaccines for children, is that correct?

Dr. MIDTHUN. It's recognized that mercury in larger amounts is a toxin. And thus, it is good to be able to reduce exposure. You can never eliminate exposure. But it is good, where you can, to be able to reduce it.

Mr. GILMAN. I will yield.

Mr. BURTON. Let me just ask, is mercury a cumulative thing in the body?

Dr. MIDTHUN. I'm not a toxicologist.

Mr. BURTON. We had one yesterday. And the toxicologist, Mr. Gilman, said that if you get a shot with mercury in it and then you get another one and another one, there's a cumulative effect. And our children are getting 26 shots by the time they go to school.

I might add, did you get a flu shot?

Mr. GILMAN. Yes, I did.

Mr. BURTON. You got thimerosal. You got mercury in your body from that shot, and Dr. Eisel, our admiral, I called him about it, and he didn't even know it was in there.

Mr. GILMAN. That raises another good question. You have taken some precautionary measures. What have you done with the public so that they're aware of these problems? What is your educational process, what have you done in the educational process to the consuming public with regard to these concerns that you have in the medical community?

Dr. MIDTHUN. Our labeling for products indicates what is in the product. In the case where there is a preservative, it is so stated. And——

Mr. GILMAN. I'm not asking just labeling. I'm asking you, have you undertaken educational initiatives for the consuming public so they'd be aware of these problems?

Dr. MIDTHUN. We believe that the vaccines are safe and effective, including those vaccines that were licensed with thimerosal as a preservative, sir.

Mr. BERNIER. Mr. Gilman, if I might add something, because we've discussed this at CDC in anticipation that we might have this question. I think one of the things that CDC has done, at least, is we generally try to work with the provider community to try to provide information about these matters. So in the last 22 months, during the time when this episode has been ongoing, there have been repeated publications, for example, in the morbidity and mortality weekly report at CDC, there have been joint statements between the Government agencies and the American Academy of Pediatrics and the American Academy of Family Physicians.

So we have worked to put information in the hands of the providers, so that they could address the concerns of the parents. Also, we have had on our Web site information about these matters. We have a hot line where parents can obtain information. So I wouldn't want to leave the impression that we haven't been proactive, if you will, about putting information out there. Because I think we have been.

Mr. GILMAN. Well, you're saying you're putting it in the hands of the providers. What about the consuming public? What are you doing? You're a government agency. What are you doing about educating the public about these dangers? What has been done by your agency or any of the panelists who are here representing our government agencies? What's been done to make the consuming public aware of these mercury problems?

Mr. BERNIER. Well, like I said, at least speaking for CDC, traditionally we make, we work through the providers to address the concerns of the parents to make sure——

Mr. GILMAN. You don't go beyond the provider? If the provider fails to make the information available, you're satisfied?

Mr. BERNIER. Well, we have also the vaccine information statements that parents are given prior to vaccination, and that's one direct connection that we have with the parents at the time of vaccination.

Mr. GILMAN. Are these statements that your agency makes to the parent?

Mr. BERNIER. Are they what, sir?

Mr. GILMAN. Are these statements that you make available to the parent?

Mr. BERNIER. Yes.

Mr. GILMAN. How is that distributed?

Mr. BERNIER. These are widely available, they're required by law to be made available to all the parents when children are immunized, before every immunization——

Mr. BURTON. If the gentleman would yield.

Mr. GILMAN. I'd be pleased to yield.

Mr. BURTON. And then we'll get to Dr. Weldon.

Mr. Gilman, do you ever use a nasal spray?

Mr. GILMAN. No.

Mr. BURTON. Does your wife, or any of their friends?

Mr. GILMAN. My wife does.

Mr. BURTON. Do you know that most nasal sprays have thimerosal in them?

Mr. GILMAN. I didn't know that.

Mr. BURTON. Yes. There's mercury in a great many products that we use as adults. And there's a tremendous rise in the number of cases of Alzheimer's. And mercury has a debilitating impact on the brain, as you saw, you probably didn't see it, in that Calgary study. So it's not only the children that are being affected by this, in my opinion. And I'm not a scientist. It's all of us.

Because we're getting mercury through the environment, but we're getting it in nasal sprays, and the health agencies, not too long ago, took mercury out of all topical dressings, because they said it would leach into the skin and cause problems. And yet, it's in nasal sprays, it's in a lot of products we use as adults, and it's in our vaccinations, like the flu shot that you received.

Mr. GILMAN. Mr. Chairman, if I might reclaim my time. It would seem to me there's a responsibility by our agencies, whether it be NIH, whether it be CDC, whatever agency is involved in regulating our vaccines, that we make more information available to the public of the dangers of mercury, and make it available not only just to potential users of the vaccine, but to the entire public.

So I'm urging those panelists who are here today to address that problem, since it is a problem that can affect millions and millions of our population.

Just one other question, Mr. Chairman. Parents are becoming concerned about the vaccines that are already on the market that have not been recalled, but many are unaware what's being done to make some recall or are unaware of your preventive actions or your concerns, because you have directed the manufacturers to take some steps to remove this product.

But what have you done with the product that's still on the shelves around the country?

Dr. MIDTHUN. It remains on the shelves, sir.

Mr. GILMAN. And could be used?

Dr. MIDTHUN. And could be used, that's correct.

Mr. GILMAN. Shouldn't you have some responsibility to remove that, if you are concerned about its use?

Dr. MIDTHUN. Again, as I mentioned, there are certain conditions that allow us to make a mandatory recall. And that is not one of them. You have to have an imminent or substantial hazard to the public health in order to make a recall.

Mr. GILMAN. Are you concerned that if some of these products are used, they could cause some problems in the health of young people?

Dr. MIDTHUN. The evidence does not show that there is a causal relationship between thimerosal as used in vaccines and autism.

Mr. GILMAN. And yet you recommended that it not be used in future manufacturing, is that correct?

Dr. MIDTHUN. That's correct, because if we can decrease exposure to mercury in ways that are available to——

Mr. GILMAN. If you're concerned about the increase in exposure, then why not take these products off the shelves and prevent their distribution? If you really are sincerely concerned about the use of these products, it would seem to me there's an absence of responsibility here by your agency.

Dr. MIDTHUN. We have to follow the regulations as they are written, sir.

Mr. BERNIER. Mr. Gilman, could I add, I want to, I think, try to correct an impression that I think is being generated here. That is that the vaccine is not being recalled then nothing's happening. I think nothing could be further from the truth. Please allow me to just take a minute to explain what has changed between, in the last 22 months and today. And a lot has changed.

I think the impression is, well, if we don't accomplish a recall that somehow this problem is not being addressed. And I think there are two or three things I'd like to point out.

Mr. GILMAN. Doctor, if I might interrupt, when we have faulty tires on vehicles, we demand that they be recalled. If we have a medication that's on the shelf that could create some problem, it would seem to me there's enough evidence, even though it's not fully explored, that there's enough evidence available that these products should not be allowed to go out to the consuming public.

Mr. BERNIER. Mr. Gilman, we have no faulty vaccines on the shelves.

Mr. GILMAN. You've already testified before us, at least Dr. Midthun has testified that as a preventive measure, they're recommending to the producer not to use this product. It would seem to me that's enough evidence to take the rest of the product off the shelf.

Dr. MIDTHUN. We've not recommended that a product not be used. We have worked with manufacturers to reduce the use of thimerosal as a preservative in vaccines.

Mr. GILMAN. And you've done that because you have a concern about the future health of young people, isn't that correct?

Dr. MIDTHUN. We have concerns about overall exposure to mercury from all sources in the environment. And this happens to be a source that we can control by switching to single dose vials in large part.

Mr. GILMAN. And these other products that are still on the shelf could contribute to their poor state of health, is that right?

Dr. MIDTHUN. We do not believe that the products out there, we believe that they are safe products, sir.

Mr. GILMAN. No further questions.

Mr. BURTON. Dr. Weldon.

Dr. WELDON. Thank you, Mr. Chairman. I want to thank all the witnesses for testifying. I certainly thank your efforts in trying to answer and address the issues and concerns we have.

Dr. Rennert, you testified, I believe, that the total spending at NIH will be $52 million on autism related research? Correct me if I'm wrong, that is including a lot of autism related research, but the actual figure on autism specific research is smaller than that, is that correct?

Dr. RENNERT. I can't tell you that for sure. I will tell you that the list we submitted is correct. We will go back and review it and provide you with the information.

Dr. WELDON. Yes, I would like you to personally provide that to me, because I have had people come to me and say the net was cast pretty wide to come up with a figure that high, and that the figure for autism specific research is actually about a third or less of that.

And the reason I bring that up is, I had my staff pull a Congressional Research Study on AIDS. The figures that were provided to me from CRS is that there's 300,000 Americans currently suffering with AIDS, and 115,000 living with HIV. Now, I realize some people estimate that those figures are quite a bit higher, and that there's a substantial cohort in the population who have exposure to HIV, they're carrying HIV and they don't know it.

But if we use those figures and those figures have appeared in the media, that's about 415,000 people. The Federal expenditures on research and treatment and the various care for those patients with AIDS is $10.9 billion. Now, if we just look at the research number, I have a figure of $3.1 billion in the year 2000. I could not get the 2001 figure.

Now, I'm told we have about a similar number of kids with autism. That's also very debatable, if you look at autism spectrum disorder, you get a much larger number. When I do the math, it comes out to, for research, about $7,000 per person with AIDS and about $140 for each child with autism. Another way to look at that figure is for every $7 we spend on AIDS related research, we're spending 14 cents on autism related research.

Do you, and I would ask any of the panelists to comment on this, do you feel that, and I feel the ultimate responsibility for this rests with the Congress, not with you, OK? So I'm not trying to make you feel bad. I think we have a responsibility to make sure that our money is spent, or the public's money, the taxpayer money, is spent appropriately. Do you think this is an appropriate level of funding, a relatively appropriate level of funding?

Dr. RENNERT. You've evoked my bias as a pediatrician. I believe our future is with our children. What I can tell you is that we will spend more money on autism research. The numbers that I've presented, regardless for the moment of the magnitude, represent an increase in funding at least in recent times, for this area. And I certainly subscribe to the notion that this is an area that should be an area of focus and emphasis for us.

Dr. WELDON. Well, does anybody else want to comment?

Dr. BOYLE. Sure, I'd be happy to.

Dr. WELDON. Are there adequate levels of funding for the types of research studies that need to be done on this?

Dr. BOYLE. We direct money at CDC as directed by Congress. But I can tell you that in the last year, we have gotten a substantial increase in our funding for autism. And that's really allowed us to develop the State surveillance, State monitoring programs that I referred to in my testimony. It's allowing us to develop the infrastructure to actually be doing a very large study of the epidemiology of autism.

So I feel that we have made substantial progress. But we have a lot further to go.

Mr. GILMAN. Would the gentleman yield?

Dr. WELDON. I'd be happy to yield.

Mr. GILMAN. Have any of you made a request for additional moneys that have not been allocated for your autism research? Have any of your agencies made a request for additional sums in the budget that were not allocated to you? Or were you all satisfied with the way the funds were being allocated?

Dr. WELDON. If I could ask it a different way, were all of your requests granted to you by your superiors within the agencies you work in?

Dr. MIDTHUN. May I just say that FDA, and the Office of vaccines, we don't have the ability to ask for funding for studying autism per se. Our mission is to regulate vaccines.

Dr. WELDON. What about CDC and NIH?

Dr. RENNERT. The answer for NIH is no.

Dr. WELDON. We'll make sure your future is secure in the year ahead.

Dr. Boyle, I've got to ask you a question related to what you're doing. We had a physician testify yesterday about this increasing incidence issue. And I think you came into my office once and we talked about this, and the change in the diagnostic manual. He made a very good point. Where are all the adults? If the prevalence isn't increasing, if the incidence isn't increasing, then where are all the adults? In all of these studies, you're looking at prevalence and incidence. Are you looking at prevalence in adults to try to make a determination to answer that question, is the rate increasing?

Dr. BOYLE. Our studies have been directed at children. We primarily look at school age children, children age 3 to 10. That is a very good question. And as may have come up yesterday, the prevalence, we call it prevalence only because we think most of it has to do with sort of prenatal etiology, so that someone is either born with the condition or with the specific genetic predisposition for the condition. So we thought we'd refer to prevalence.

Dr. WELDON. Well, I would recommend you look at that issue, looking at the disease prevalence throughout all age groups in the population. Because I think that's a very, very critical question, if we are going to try to get——

Dr. BOYLE. I think Dr. Amaral testified yesterday about efforts in California to address the issues of sort of changes in diagnosis, as many researchers have suggested, as well as the greater awareness of the condition and the impact that has had on the increase in the number of cases seen in California. Actually, I think that's going to be a very interesting study. It's really going to be able to shed some light on what's happening.

Mr. BURTON. Can we come back to you, Dr. Weldon? Mr. Waxman is here and he wants to ask a few questions, then we'll come right back to you.

Mr. WAXMAN. Thank you, Mr. Chairman.

Dr. Bernier, the CDC has explained that it is opposed to recalling thimerosal-containing vaccines because it's concerned about shortages. In fact, I understand there is a concern about a shortage of DTaP vaccines. At the hearing yesterday, one of the witnesses suggested that stocks of non-thimerosal vaccines are adequate and that there was no need to keep thimerosal-containing vaccines on the shelves.

Can you explain your concerns about shortages? For instance, if the DTaP vaccine containing thimerosal were recalled, what possible effect would that have on our children?

Mr. BERNIER. Yes, Mr. Waxman, it is correct that at the present time, for DTaP, there is a very tight supply situation. We have two additional manufacturers that have left the market in the recent past, and we are now left with only two manufacturers. And there are back orders at the present time that cannot be filled because the amount of available vaccine is not adequate to fill those back orders.

So if in fact there was to be issued a strong preference for thimerosal free DTaP, or if there were to be a sudden recall of the existing DTaP vaccine with thimerosal, this would produce spot shortages which would create, we think, delays in children being immunized, which could lead to disease very quickly.

In 1999 alone, there were 15 deaths from pertussis in the United States. This year already we've had five deaths from pertussis. So the need to continue the coverage with DTaP is very real. These are not hypothetical or theoretical risks. We know that creating shortages will produce coverage problems, will increase the risk of children to these diseases.

Mr. WAXMAN. Last year, CDC testified that they were actively monitoring possible adverse effects of thimerosal, the mercury-containing preservative that's being phased out of vaccines. CDC found no link between thimerosal and developmental delays. Have you continued to monitor for any of these effects, and what has your surveillance shown?

Mr. BERNIER. Well, we have continued at least in the look at the autism question. In the original results from the vaccine safety data link, there was no evidence of a link between thimerosal exposure and autism. In the last year, an additional number of cases has accumulated. I believe somewhere in the vicinity of an additional 40 cases. When we add those cases to the ones that we looked at before, we reached the same conclusion. It has not altered the original conclusion, which was that there was no link between exposure to thimerosal and autism.

Mr. WAXMAN. Thank you. Dr. Midthun, at the hearing yesterday Dr. Haley testified about the toxicity of thimerosal-containing vaccines. He suggested that the thimerosal in vaccines was harmful to children.

In the pre-licensure phase, is the vaccine tested for toxicity?

Dr. MIDTHUN. Yes, it is. The vaccines are usually evaluated in a very large number of infants, if that's the target population for whom they're intended. They are tested with regard to the entire formulation. And thus, if there were to be any acute toxicity, that would be noted in the clinical trials that are done in support of the license application.

Mr. WAXMAN. Does this mean that the entire vaccine, including all of its component parts, is tested for toxicity?

Dr. MIDTHUN. That's correct. The vaccine in entirety is tested.

Mr. WAXMAN. So if a vaccine were toxic, this should be revealed in the prelicensure phase, is that correct?

Dr. MIDTHUN. Yes, that's correct.

Mr. WAXMAN. What did the toxicity testing of vaccines with thimerosal reveal? Did this testing indicate that the thimerosal is likely to pose health dangers for children?

Dr. MIDTHUN. The clinical studies did not suggest that, sir.

Mr. WAXMAN. So why did the FDA move quickly to remove thimerosal from vaccines?

Dr. MIDTHUN. Because we felt it was an achievable goal. It was a way where we could reduce the overall exposure to mercury among children, and it was something that was achievable, because we could switch from multi-dose to single dose vials. In the United States that was something that was feasible.

Mr. WAXMAN. Dr. Boyle, Dr. Wakefield testified at yesterday's hearing that we need active surveillance of vaccine adverse events. Can you explain what CDC does to actively monitor potential problems associated with vaccines?

Mr. BERNIER. CDC is actively looking at vaccine safety events through the VAERS system. We are monitoring events and when events occur that create cause for concern, we have the resource represented by the vaccine safety data link population, which is a way of, provides us an easier means of testing hypotheses that may arise from adverse events that are detected.

So we have this detection arm and then we have a testing arm where we can test hypotheses. For example, this was one of the ways in which it worked recently with rotavirus and intussusception, where both arms of the vaccine safety mechanisms were put into play in order to address that concern.

Mr. WAXMAN. Thank you very much. Thank you, Mr. Chairman.

Mr. BURTON. Let me just followup on what Mr. Waxman said. I know he has to leave and he's probably not going to hear the response, but did you folks test the rotavirus vaccine before you put it out on the market?

Dr. MIDTHUN. I've not been involved with the rotavirus vaccine trials.

Mr. BURTON. It was tested by FDA, wasn't it?

Dr. MIDTHUN. It was tested by FDA.

Mr. BURTON. And in 9 months it was recalled, wasn't it?

Dr. MIDTHUN. Maybe I could ask Dr. Baylor. I wasn't there at the time.

Mr. BURTON. You don't have to ask him. It was recalled, because one child died, there were several serious problems, intestinal problems where there was surgery involved. And it was recalled.

Dr. MIDTHUN. I just spoke with Dr. Baylor. It wasn't actually a recall, either a mandatory or a voluntary recall. The company decided to withdraw it from the market, sir.

Mr. BURTON. Well, because one child died, and a whole host of them were injured. I mean, you know, you can cut it either way you want to. The fact is, they took it off the market, and it had been tested. So you folks are not infallible.

Now, the DPAT shot, are they still manufacturing that with thimerosal in it?

Mr. BERNIER. No, Mr. Chairman, they are not.

Mr. BURTON. They're not. But you say that they're not producing enough of the single shot vaccines to take care of the needs of the country at the present time?

Mr. BERNIER. At the present time, there is a shortage in the supply, correct. They are back ordered, and the new vaccine that they are producing is not adequate to meet the demand at the present time.

Mr. BURTON. How long will it take for that to be adequate?

Mr. BERNIER. I think the FDA could have a better idea of that. My impression is that it's, well, I mean, relatively short, and I'm thinking of a few months. But I don't have the information.

Mr. BURTON. So in a few months, they could have the supply up. Now——

Mr. BERNIER. Could we just get FDA, because I don't want that to be on the record, if that's true or not.

Mr. BURTON. How long will it take for them to get the single shot vials, doses up to safe level?

Dr. MIDTHUN. I can't give you the exact time line. But I do know that there are two more lots potentially containing thimerosal that the company intends to release. But after that, they will then be releasing only the thimerosal reduced versions.

Mr. BURTON. How many shots are in a lot?

Dr. MIDTHUN. That's proprietary information, sir.

Mr. BURTON. Do you want me to subpoena it?

Dr. MIDTHUN. I would be happy——

Mr. BURTON. You get it for me, or I'll subpoena it. I want it.

Dr. MIDTHUN. I would be happy to respond to the chairman's letter on that.

Mr. BURTON. Because what we're talking about, there's thousands and thousands of shots of DPAT that you're going to put into the system and kids are going to get those shots because of the shortage.

Now, let me ask you, what's the likelihood, let's say it takes 6 months, let's say it takes 6 months to get the single shots up to snuff to where you've got a supply, let's say it takes 6 months. How many kids do you think are going to die in 6 months because they don't get that shot?

Mr. BERNIER. I can't estimate, Mr. Chairman. I can tell you that as I mentioned earlier in my testimony, this is not hypothetical. In 1999, there were 15 deaths associated with pertussis. And already, there have been five deaths this year. So if we created a situation where we abruptly said, you must use thimerosal free vaccine, that would create shortages which would lead to delays which would lead to what I'm calling days of lost protection.

Mr. BURTON. I understand. You've made your point. Let me just say this. I want the names of the producers of the DPAT shot. And I'm going to subpoena records from them to find out how much is in a lot, how they have two more lots that they have to use, they have two more lots. I want to find out how long it would take for them to produce the diphtheria, tetanus and the pertussis vaccines individually. I'm going to find out how long it's going to take.

Because I suspect that those lots have a lot of shots in them and there's a lot of money involved, a lot of money involved. And as a result, they want to sell those before they go ahead and get their lots of individual shots up to snuff. And I think it's money, I really believe that.

I think that there is mercury in those vaccines, and during the time that you say two or three or four or five or six or seven children are going to possibly die, and we don't want any child to die, according to my figures, there are 16 children a day that's going to come down with autism. A day. That's 17,520 children are going to be at risk for autism in the next 3 years while studies are going on, if mercury has something to do with it, as many, many people believe.

Scientists, toxicologists, it's not just me. We had a whole litany of doctors from all over the world talking about this yesterday. And what you're saying is one thing. But what scientists and doctors and studies have already shown is that mercury does have a debilitating impact on the brain. So you're talking about children at risk. In 3 years that it's going to take to go through these studies, 17,520 children are likely to become autistic. If you folks are wrong, how are you going to live with yourselves?

The gentlelady is recognized.

Ms. ROS-LEHTINEN. Thank you so much, Mr. Chairman. I regret that I have not been able to be here for the entire hearing due to an overbooked schedule. But I have the testimony and I look forward to reading it tonight. As I had said before, we have two good friends of our family, Charles and Patience Flick, who have two children who are afflicted with autism. I know what a terrible toll autism can take on a family. Everything that the Flick family does is related and surrounded by Bonnie and Willis and their care and what will happen to them. And any steps the Flick's take, Bonnie and Willis are at the foremost of their thoughts.

Bonnie is a little more high functioning and was able to go to Disney World with us. Willis is unfortunately so overstimulated by the environment that he can barely leave his house. Everything is too much sight and sound for him. So I look forward to seeing the fruits of the pressure that Chairman Burton is bringing to bear on this issue. We need to improve research dollars, and have more research going into the causes of autism, to help lead us to a cure. Because I know how devastating that affliction is, not just on the children who have it, but on their families.

We look forward to getting more evidence about the relationship between vaccinations and the rise, dramatic rise in autism rates. I know that many are not in agreement with that, but I congratulate Chairman Burton for his steadfast devotion and his bravery, in spite of all of the attempts of the scientific and health community trying to make this seem like there's no tie-in whatsoever. I don't think that we should leave any stone unturned. If mercury is a factor, we should give serious consideration to revamping our vaccination program and looking at other possible factors involved in the dramatic rates in autism across the country.

So I thank you, Chairman Burton, on behalf of the many Flick families throughout the United States. Thank you, Dan.

Mr. BURTON. I thank the gentlelady.

Mrs. Morella, do you have any comments or questions?

Mrs. MORELLA. Actually, I commend you for the ongoing series of hearings that you've had on autism. We all care about it. I'm really here to listen, to learn and then to do what I can to lead and I know you have medical experts before you, many of them who are involved in laboratories in my district, NIH and of course FDA, and I value CDC.

I'm also interested in the kind of funding that you do have. Really, we work very hard, just as an example, to double the funding for NIH for that 5 year plan we had, so that by 2003 we would realize it. We are well on our way, this is our 4th year. I'm curious, with regard to autism, and I must say, a lot of the leadership on looking into autism obviously has come from the chairman, although I do wear sometimes my little jigsaw puzzle ribbon which is autism, the puzzle pieces, right, which we are trying to put together.

I understand from your testimony, and I guess this would be Dr. Rennert, that $1 million is being set aside to fund innovative treatment proposals, and that you have 30 applications. How do you work with that? Are you kind of a magician?

Dr. RENNERT. No, I think one works with it by trying to fund as many grants as one can, and that the limit is the number of dollars.

Mrs. MORELLA. So how many do you think you can?

Dr. RENNERT. Well, I think again, the response I would make is that the amount of funding we could use is equivalent to the number of meritorious proposals that there are. And it depends on where you set the bar.

Mrs. MORELLA. Sounds like a political answer to me.

Dr. RENNERT. No, I can't give you a precise number. But the point is quite clearly, we could use more funding to fund more proposals and more research on autism.

Mrs. MORELLA. It just seems to me that of the 30 applications and obviously probably not all would meet the qualifications, the peer review, what it goes through, but certainly $1 million isn't going to fund more than a couple of them, probably.

Dr. RENNERT. Three to four is what that would fund.

Mrs. MORELLA. So it does say something about the need for us to begin to look more into that in terms of the adequate funding.

Then I note also, looking at Dr. Boyle's testimony, and I wasn't here to hear you synopsize it for the committee, but you mentioned that CDC, NIH and 10 NIH funded centers and programs of excellence in autism are collaborating on a case control study of developmental regression. Each of these centers was awarded funds through the NIH competitive process.

Can you give us like a time line on it, how that is going?

Dr. BOYLE. Actually, I may let my colleague at NIH address that.

Dr. RENNERT. Again, the program was initiated in 1997. And at this point in time, as we mentioned in our testimony, there are approximately 2,300 patients with well defined autism that are a part of the network and the study. The second part is with regard specifically to the question of the temporal association between vaccination and the onset of autism, as well as a study of the potential effects of mercurials in vaccines as preservatives.

There are at the present time 1,600 cases that are being used for the study. And the phase one part of the study will look at 250 cases of patients with early onset autism, 250 patients with regressive autism, and a corresponding number of controls for each group. That work now is in the second phase where the analysis will begin and the study of the biological specimens that were obtained.

A third part, because you mentioned it in regard to funding, I forgot to point out though it was in my written testimony, that in fact we will release in the coming year an RFA or request for applications for the competitive renewal and the commitment to renew these centers for another 5 years. Clearly, our hope will be that over time, that we could add more centers to this. But specifically, the element of study that ought to be completed, as I was asked by Chairman Burton in the next 2 years or so, is that these studies linking or attempting to establish whether there's an association or what the association is between vaccination and thiomercurials will be completed.

Mrs. MORELLA. Within 2 years, then, that's what you're saying, 2 to 3 years. Fine. Thank you, Mr. Chairman.

Mr. BURTON. Let me just say to the gentlelady, in 3 years is what we thought was going to be the study, but if we waited 3 years to have a conclusion drawn, and we continue to use these kinds of vaccines, we're all for vaccinations, but not with some of these things like mercury in them, there would be 17,520 new children that would probably be autistic. That is if mercury did have something to do with it.

I think we're about to wrap this up. We have a number of questions we'd like to submit to you for the record. I don't want to keep you here all day. Do we have any parents that have autistic children in the room? Would you raise your hands?

How many of you believe that your children were adversely affected by something in the vaccines? Would you raise your hands? Is that everybody or almost everybody? About 80 percent; 8 out of 12, maybe 9 out of 12. That's what we're getting in e-mails by the hundreds and thousands.

Now, maybe you folks are right, maybe mercury doesn't have anything to do with it. Maybe the thimerosal doesn't. But they think it does. And there's a growing body of these people. And they're getting organized all across the country, and so is the Congress of the United States. So I really hope that you'll take a hard look at this. Because it isn't going to go away. And as I said before, it's going to cost this country trillions of dollars.

In any event, do you have any other questions?

Mrs. MORELLA. No, I don't, but of course I hope on the basis of all of this that if you can expedite so that we can come to some conclusions, because I can recognize the passion, but also the desire for patience that's so difficult for the chairman. And I would agree with him, if it's been going on since 1997, we should have some results. Thank you very much.

Mr. BURTON. Thank you, Congresswoman Morella.

We will submit these for the record.

There are documents that we'll be requesting. If there's a problem with you giving those because of confidentiality of any kind, if you would let us know and we'll be happy to legally send a subpoena to get that information, because we want to make sure we have as much research material as possible.

We'd also like to know who are the manufacturers of the DPAT shot.

Dr. MIDTHUN. I believe Ms. Clay has that.

Mr. BURTON. OK. We'll be contacting them to get records on the supply that they have and how long it will take to go to single shot vials.

With that, thank you for being here. We stand adjourned.

[Whereupon, at 11:45 a.m., the committee was adjourned, to reconvene at the call of the Chair.]

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